Transition-metal-catalyzed enantioselective synthesis and functionalization of 1,2- and 1,4-BIS(boronate)esters

Author: Heather Elizabeth Burks

Boston College

The Graduate School of Arts and Sciences

Department of Chemistry

TRANSITION-METAL-CATALYZED ENANTIOSELECTIVE SYNTHESIS AND FUNCTIONALIZATION OF 1,2- AND 1,4-BIS(BORONATE)ESTERS

a dissertation

by

HEATHER ELIZABETH BURKS

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ABSTRACT

TRANSITION-METAL-CATALYZED ENANTIOSELECTIVE SYNTHESIS AND FUNCTIONALIZATION OF 1,2- AND 1,4-BIS(BORONATE)ESTERS

by

HEATHER ELIZABETH BURKS

Dissertation Advisor

Professor James P. Morken

The first examples of an enantioselective allene diboration and diene diboration are reported. The asymmetric palladium-catalyzed allene diboration afforded 1,2-bis(boronate)esters in up to 98% ee. The reaction development for the allene diboration, as well as the expansion of the substrate scope, and elucidation of the reaction mechanism are reported. Following the development of the enantioselective allene diboration, the first enantioselective diene diboration was disclosed. 1,4-Dihydroxylation products resulting from a tandem diene diboration/oxidation sequence are obtained in up to 92% ee.

In memory of:

My grandmother Betty Lou Hill and my great-grandmother Juanita Louden

Dedicated to:

My grandfather George Hill, Jr.

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LIST OF ABBREVIATIONS AND SYMBOLS

Å	angstrom
Ac	acetate
acac	acetylacetonate
aq	aqueous
$B_2(cat)_2$	bis(catecholato)diboron
$B_2(pin)_2$	bis(pinacolato)diboron
BINAP	2,2-bis(diphenylphosphino)-1,1'-binaphthyl
brine	saturated sodium chloride
*n*BuLi	*n*-butyl lithium
^oC	degrees Celsius
^{13}C NMR	carbon nuclear magnetic resonance spectroscopy
CAA	alpha-cyano-4-hydroxy-cinnamic acid
cat	catechol
cat.	catalytic
$CDCl_3$	deuterated chloroform
CH_2Cl_2	dichloromethane
CI	chemical ionization
cm^{-1}	wavenumber
cod	cyclooctadiene

DART	direct analysis in real time
dba	dibenzylideneacetone
DEAD	diethyl azodicarboxylate
deg/min	degree per minute
DIAD	diisopropyl azodicarboxylate
DIBALH	diisobutyl aluminum hydride
dppb	1,4-bis(diphenylphosphino)butane
dppf	bis(diethylphosphino)ferrocene
d.r.	diastereomeric ratio
ee	enantiomeric excess
EI	electron impact
eq.	equation
equiv	equivalents
ESI	electrospray ionization
g	gram
GLC	gas liquid chromatography
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
^{2}H NMR	deuterium nuclear magnetic resonance spectroscopy
h	hour
HCl	hydrogen chloride
H-MOP	(*S*)-2-diphenylphosphino-1,1'-binaphthyl
H_2O_2	hydrogen peroxide

HRMS	high resolution mass spectrometry
IR	infrared spectroscopy
K_2CO_3	potassium carbonate
$KMnO_4$	potassium permanganate
L	liter
$LiBH_4$	lithium borohydride
LRMS	low-resolution mass spectrometry
M	molar
MADLI	matrix assisted laser desorption ionization
MCP	methylenecyclopropane
MeI	methyl iodide
MeOD	methanol-d_1
MeOH	methanol
mg	milligram
$MgSO_4$	magnesium sulfate
MHz	mega hertz
min	minute
mL	milliliter
mmol	millimole
mol %	mole percent
NaHMDS	sodium bis(trimethylsilyl)amide
NaOH	sodium hydroxide

Na_2SO_4	sodium sulfate
$Na_2S_2O_3$	sodium thiosulfate
nbd	norbornadiene
NBSH	2-nitrobenzenesulfonylhydrazide
NHC	N-heterocyclic carbene
NMO	4-methylmorpholine N-oxide
^{31}P NMR	phosphorus nuclear magnetic resonance spectroscopy
Pd	palladium
PDC	pyridinium dichromate
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium
PEt_3	triethylphosphine
pin	pinacol
PMA	phosphomolybdic acid
PPh_3	triphenylphosphine
$^{i}PrOH$	isopropanol
psi	pounds per square inch
Pt	platinum
$Pt_2(dba)_3$	tris(dibenzylideneacetone)diplatinum
R_f	retention factor
Rh	rhodium
rt	room temperature
S-PHOS	2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl

SFC	supercritical fluid chromatography
S-QUINAP	(*S*)-(-)-1-(2-diphenylphosphino-1-naphthyl)isoquinoline
t-	*tert*-
TADDOL	(*4R,5R*)-(-)-2,2-dimethyl-α, α, α', α'-tetraphenyl-1,3-dioxolane-4,5-dimethanol
THF	tetrahydrofuran
TOF	time-of-flight
o-tol	*ortho*-tolyl
p-tol	*para*-tolyl
TPAP	tetrapropylammonium perruthenate
TMS	trimethylsilyl
μL	mircoliter
μmol	mircomole
UV	ultraviolet
xylyl	3,5-dimethylphenyl
% y	% yield

Chapter 1

Catalytic Enantioselective Diboration, Disilylation and Silylboration: New Opportunities for Asymmetric Synthesis

1.1. Introduction

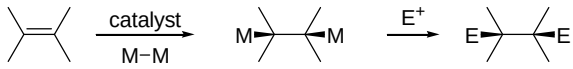
Organoboranes and organosilanes are versatile reagents for organic synthesis, due in part to a combination of accessibility, stability, and reactivity. For example, while the majority of organoboronic esters are stable to air and moisture, under the appropriate reaction conditions they participate in oxidation, amination, sulfination, phosphination, halogenation and a variety of catalyzed and non-catalyzed carbon-carbon bond forming reactions.[1] While the number of synthetic transformations available to functionalize organosilanes is not as extensive as organoboronic esters, protodesilation,[2] oxidation,[3] and cross-coupling[4] are effective transformations that rapidly build molecular complexity.

To construct densely-functionalized organoboranes for use in synthesis a number

(1) (*a*) Phosphination and sulfination: Draper, P. M.; Chan, T. H.; Harpp, D. N. *Tetrahedron Lett.* **1970**, *11*, 1687. Catalytic cross-coupling: (*b*) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147. Review including all other reactions, see: (*c*) Kohta, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (*d*) Brown, H. C.; Singaram, B. *Pure Appl. Chem.* **1987**, *59*, 879. For a recent review describing reactions of organoboronic esters, see: (*e*) Crudden, C. M.; Edwards, D. *Eur. J. Org. Chem.* **2003**, 4695.
(2) (*a*) Hudrlik, P. F.; Hudrlik, A. M.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 6809. (*b*) Heitzman, C. L.; Lambert, W. T.; Mertz, E.; Shotwell, J. B.; Tinsley, J. M.; Va, P.; Roush, W. R. *Org. Lett.* **2005**, *7*, 2405. (*c*) Honda, M.; Mikami, Y.; Sanjyo, T.; Segi, M.; Nakajima, T. *Chem. Lett.* **2005**, *34*, 1432.
(3) Review: Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599.
(4) Hatanaka, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1990**, *112*, 7793.

of catalytic reactions may be used. The addition of B_2Cl_4 to unsaturated substrates has been known for many years, and within the past 10 years, catalytic versions of the addition of dimetalation reagents have been developed.[5] Very recently, the catalytic asymmetric addition of diborons,[6] disilanes,[6] and silylboron[6] reagents to π-systems has emerged (Scheme 1.1). In connection with these reactions, the functionalization of the organo-element bond, through the addition of the appropriate reagent, would facilitate the ability to install molecular diversity in a limited number of synthetic steps.

Scheme 1.1. Addition of Dimetalation Reagents to π-Systems



1.2. Background

The majority of dimetalation reactions may be summarized by three generalized reaction mechanisms.[7] The most common mechanism for dimetalation of π-systems is depicted in Scheme 1.2. Oxidative addition of the dimetalation reagent to the transition metal, followed by substrate coordination, insertion, and reductive elimination affords the desired product, and subsequently regenerates the transition-metal catalyst.

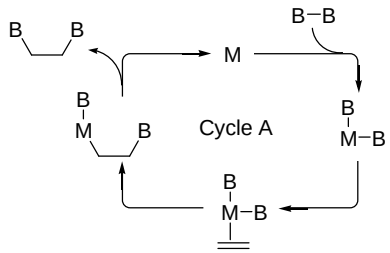
---

(5) Reviews on element-element additions, see: (*a*) Beletskaya, I.; Moberg, C. *Chem. Rev.* **2006**, *106*, 2320. For reviews on diboration, see: (*b*) Ishiyama, T.; Miyaura, N. *Chem. Record* **2004**, *3*, 271. (*c*) Marder, T. B.; Norman, N. C. *Topics in Catalysis* **1998**, *5*, 63. For a review on disilylation, see: (*d*) Sharma, H. K.; Pannell, K. H. *Chem. Rev.* **1995,** *95*, 1351. For a review on silylboration and disilylation see: (*e*) Suginome, M.; Ito, Y. *Chem. Rev.* **2000**, *100*, 3221.

(6) For a recent review on enantioselective diboration, disilylation, and silylboration, see: Burks, H. E.; Morken, J. P. *Chem. Commun.* **2007**, 4717.

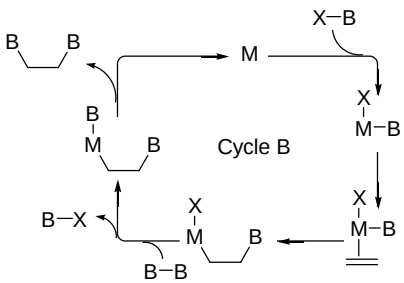
(7) There are exceptions to these generalizations. For example, see: Ogoshi, S.; Tomiyasu, S.; Morita, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2002**, *124*, 11598.

Scheme 1.2. Generalized Catalytic Cycle for Oxidative Addition of Dimetalation Reagents



The second generalized reaction mechanism for the dimetalation of unsaturated compounds does not involve oxidative addition of the dimetalation reagent to the transition-metal catalyst (Scheme 1.3). Instead, in a mechanism put forth by Cheng and co-workers, transition-metal-catalyzed dimetalation is initiated by oxidative addition of a boron/silicon halide to the catalyst.[8] As depicted in cycle B, oxidative addition of the boron-halide to the transition-metal catalyst is followed by substrate coordination and insertion. Transmetalation between this intermediate and the dimetalation reagent regenerates the boron/silicon halide, as well as a metal-bis(boryl) intermediate that is situated for reductive elimination to afford product.

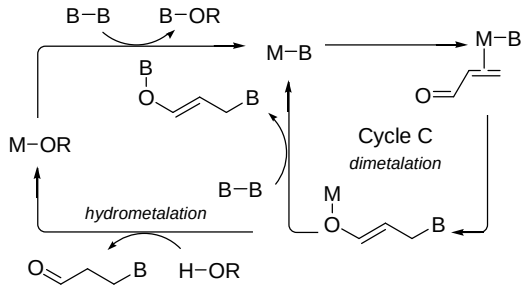
Scheme 1.3. General Catalytic Cycle for Oxidative Addition of a Boron/Silicon Halide



(8) (*a*) Chang, K. -J., Rayabarapu, D. K.; Yang, F. -Y.; Cheng, C. -H. *J. Am. Chem. Soc.* **2005**, *127*, 126. (*b*) Yang, F. -Y.; Cheng, C. -H. *J. Am. Chem. Soc.* **2001**, *123*, 761.

The final generalized reaction mechanism for dimetalation differs from the previous two mechanisms in that it does not rely on oxidative addition of any reagents (Scheme 1.4).[9] This cycle applies to activated alkenes and begins with a metal-boryl species which coordinates to the substrate (cycle C, dimetalation). Substrate insertion into the M-B bond delivers a metal-enolate that undergoes transmetalation with a dimetalation reagent to complete the catalytic cycle. In some cases, hydrometalation of the metallo-enolate may occur, generating the β-boryl carbonyl and a metal alkoxide (cycle C, hydrometalation). In this circumstance, transmetalation between the metal alkoxide and the interelement reagent regenerates the metal-boron catalyst, which subsequently re-enters the catalytic cycle.

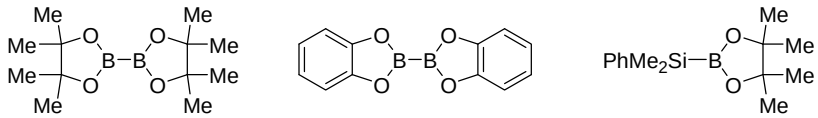
Scheme 1.4. Generalized Catalytic Cycle Not Involving Oxidative Addition



The commercial availability of the requisite dimetalation reagents for diboration, disilylation, and silylboration is limited. Commercially available bis(pinacolato)diboron, $B_2(pin)_2$, and bis(catecholato)diboron, $B_2(cat)_2$, are commonly employed in transition-metal-catalyzed diboration reactions (Figure 1.1). A handful of other diborons are

(9) (*a*) Ito, H.; Ishizuka, T.; Tateiwa, J.; Sonoda, M.; Hosomi, A. *J. Am. Chem. Soc.* **1998**, *120*, 11196. (*b*) Clark, C. T.; Lake, J. F.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 84.

commercially available; however, their costly preparation, purification, and stability make their utility in diboration reactions less attractive. Several reports have surfaced highlighting the differences between $B_2(pin)_2$ and $B_2(cat)_2$. From a practical standpoint, $B_2(pin)_2$ is significantly more attractive to employ in diboration reactions, due to its stability in air and moisture. Additionally, it is available on a multi-kilogram scale for about $900 per kg.[10] Bis(catecholato)diboron is significantly more expensive than $B_2(pin)_2$, available for $62,000 per kg.[11]



$B_2(pin)_2$ $B_2(cat)_2$ $PhMe_2SiB(pin)$

Figure 1.1. Commercially Available Dimetalation Reagents

Reactivity differences also exist between $B_2(pin)_2$ and $B_2(cat)_2$. The rate of oxidative addition of $B_2(cat)_2$ to $(PPh_3)_2Pt(ethylene)$ is faster than with $B_2(pin)_2$.[12] The bis(boryl) intermediate derived from oxidative addition of $B_2(cat)_2$ to platinum(0) may be more stable than $B_2(pin)_2$.[13] The addition of $B_2(cat)_2$ to $(PPh_3)_2Pt(Bpin)_2$ irreversibly formed $B_2(pin)_2$ and $(PPh_3)_2Pt(Bcat)_2$.[13] In kinetic experiments conducted by Norman and Marder, the Pt-catalyzed alkyne diboration with $B_2(cat)_2$ was significantly faster than with $B_2(pin)_2$.[12] The choice of employing $B_2(cat)_2$ or $B_2(pin)_2$ in a diboration reaction

(10) This price is from AllyChem Co. Ltd. (www.allychem.com) for orders of over 100 kg. For smaller quantities the price is $995/kg.
(11) $B_2(cat)_2$ is commercially available from Sigma-Aldrich for $309/5 g.
(12) Lesley, G.; Nguyen, P.; Taylor, N. J.; Marder, T. B.; Scott, A. J.; Clegg, W.; Norman, N. C. *Organometallics* **1996**, *15*, 5137.
(13) Iverson, C. N.; Smith, M. R., III, *Organometallics* **1996**, *15*, 5155.

depends upon the transition metal employed in the reaction as well as the reactivity of the substrate.

A catalytic system may be tuned to promote diboration of unreactive π-systems by employing the more reactive $B_2(cat)_2$. On the other hand, should the diboration product need to be isolated, the use of $B_2(pin)_2$ is more desirable as these pinacol-derived bis(boronate)esters are more stable than their catechol analogs.

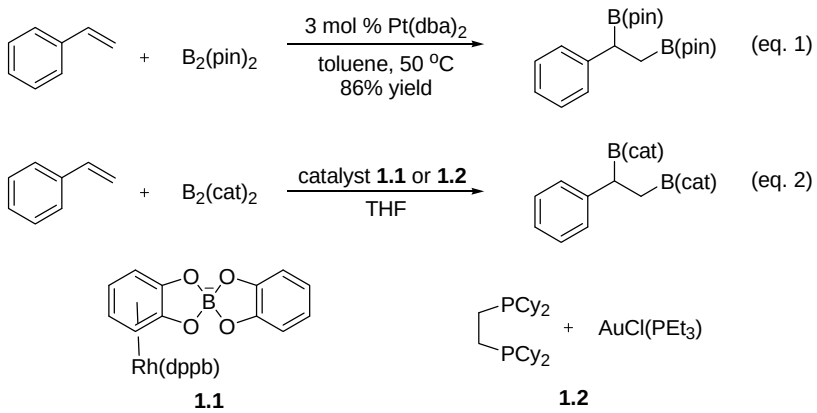
Reports of the addition of disilanes across π-bonds have increased over the last two decades. However, the number of disilanes that are commercially available and viable for the oxidative addition to transition-metal catalysts, a requisite for general catalytic cycles A and B (Scheme 1.2 and 1.3), remains limited. The rate of oxidative addition of disilanes to transition metals is enhanced by the addition of electronegative atoms to silicon, and employing sterically less encumbered substituents on silicon is also beneficial.[14] Only a handful of disilanes with these requirements are readily available. The requisite dimetalation reagents for transition-metal catalyzed silylboration reactions are limited to only one commercially available silylboron, $PhMe_2Si$-B(pin) (Figure 1.1). While the commercial availability of silylborons is limited, their preparation is relatively straightforward.[15] Analogous to disilanes, the addition of electronegative elements on silicon enhances the reactivity of these substrates toward oxidative addition to transition-metal catalysts.

(14) Sharma, H. K.; Pannell, K. H. *Chem. Rev.* **1995**, *95*, 1351.
(15) Ohmura, T.; Masuda, K.; Furukawa, H.; Suginome, M. *Organometallics* **2007**, *26*, 1291.

1.3. Unactivated Alkenes

1.3.1. Diboration of alkenes. Unfunctionalized alkenes, containing no functional groups suitable for coordination to a transition-metal catalyst, represent a challenging class of substrates for dimetalation reactions. The challenge is even more substantial when considering asymmetric catalysis. Miyaura and Suzuki reported the first transition-metal-catalyzed addition of diboron reagents to unsaturated unactivated substrates.[16] This "ligand-free" platinum-catalyzed addition of diboron reagents to alkynes was later extended to alkenes (Scheme 1.5, eq. 1); however, it left no possibility for asymmetric catalysis.[17] Reports soon followed which employed rhodium(I) and gold catalysts in the diboration of unactivated alkenes (Scheme 1.5, eq. 2);[18] however, the asymmetric variant remained elusive for quite some time.

Scheme 1.5. Platinum, Rhodium, and Gold-Catalyzed Diboration of Alkenes



(16) Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc.* **1993**, *115*, 11018.
(17) (*a*) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun.* **1997**, 689. (*b*) Iverson, C. N.; Smith, M. R., III, *Organometallics* **1997**, *16*, 2757.
(18) (*a*) Baker, R. T.; Nguyen, P.; Marder, T. B.; Westcott, S. A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1336. (*b*) Dai, C.; Robins, E. G.; Scott, A. J.; Clegg, W.; Yufit, D. S.; Howard, J. A. K.; Marder, T. B.; *Chem. Commun.* **1998**, 1983. (*c*) Nguyen, P.; Coapes, R. B.; Woodward, A. D.; Taylor, N. J.; Burke, J. M.; Howard, J. A. K.; Marder, T. B. *J. Organomet. Chem.* **2002**, *652*, 77.

In 2003, the Morken lab reported the first asymmetric transition-metal-catalyzed diboration of unactivated alkenes.[19] Complexes between rhodium(I) and (*S*)-QUINAP catalyzed the addition of $B_2(cat)_2$ to prochiral unfunctionalized alkenes. A *syn*-1,2-diol was obtained following treatment of resulting 1,2-bis(boronate)ester with alkaline hydrogen peroxide (Scheme 1.6). The rhodium-catalyzed diboration of *trans*-alkenes delivered 1,2-diols in high enantiomeric excess (up to 98% ee). Oxygen-containing *trans*-disubstituted alkenes were also converted to diols in high enantiomeric excess, as long as the oxygen was not at the allylic position. Allylic ethers formed allyl boronic esters under these reaction conditions.[20] While the rhodium/QUINAP catalyst is excellent for *trans*-alkenes, 1,1'-disubstituted alkenes and aliphatic alkenes delivered 1,2-diols of diminished enantioselectivities. In regards to aliphatic alkenes, substrates bearing a quaternary center adjacent to the alkene were more selective, affording products of high enantiomeric excess (93-95% ee). Diboration of *cis*-olefins delivered products of diminished enantioselectivities, as illustrated in the diboration *cis*-β-methyl styrene and 1,2-dihydronaphthalene. In order to increase the enantioselectivity for the diboration of mono-substituted alkenes, not bearing an α-quaternary center, various reaction conditions have been surveyed by our laboratory and by that of Ferandez;[21] however, to date a highly enantioselective process remains elusive.

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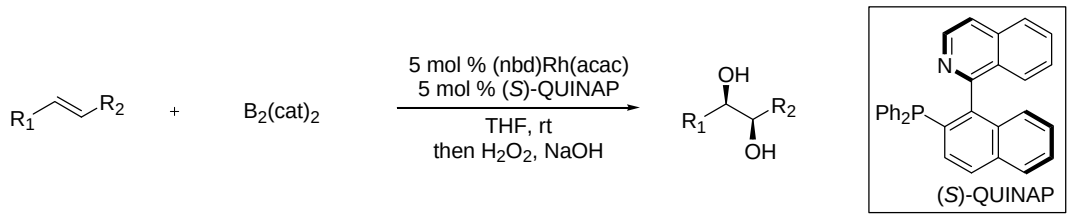
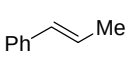
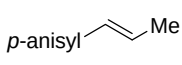
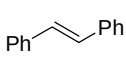
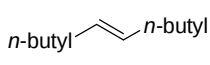
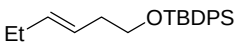
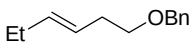
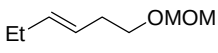
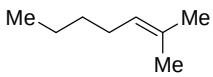
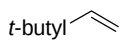
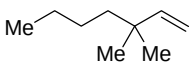
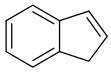
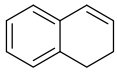
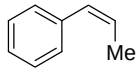
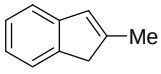
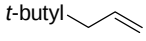
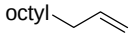
(19) (*a*) Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8702. (*b*) Trudeau, S.; Morgan, J. B.; Shrestha, M.; Morken, J. P. *J. Org. Chem.* **2005**, *70*, 9538.

(20) While this reactivity has been documented for palladium-catalysis, this is the first example with rhodium-catalysis. References for palladium-catalysis: (*a*) Ishiyama, T.; Ahiko, T.; Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 6889. (*b*) Ahiko, T.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **1997**, 811.

(21) Ramirez, J.; Segarra, A. M.; Ferandez, E. *Tetrahedron: Asymmetry* **2005**, *16*, 1289.

Scheme 1.6. Rh(I)-Catalyzed Asymmetric Diboration of Alkenes



				
71% y, 93% ee	71% y, >98% ee	48% y, 98% ee	76% y, 98% ee	67% y, 46% ee
				
62% y, 97% ee	62% y, 97% ee	68% y, 98% ee	8% y, 91% ee	47% y, 94% ee
				
82% y, 95% ee	81% y, 59% ee	68% y, 88% ee	72% y, -49% ee	61% y, -49% ee
				
17% y, 93% ee	68% y, 33% ee	79% y, 61% ee	82% y, 62% ee	

The enantioselective rhodium-catalyzed diboration of alkenes, in particular aliphatic alkenes, provides by-products resulting from β-hydride elimination. The ligand-free platinum-catalyzed diboration of alkenes, and the gold-catalyzed variant reported by Baker (Scheme 1.5), are the only two reactions that limit formation of by-products resulting from β-hydride elimination. Recent reports from Fernadez et al. are directed towards solving this problem.[22] Gold(I)-, silver(I)-, and platinum(I)-NHC catalysts were synthesized and found to catalyze the addition of $B_2(cat)_2$ to prochiral monosubstituted

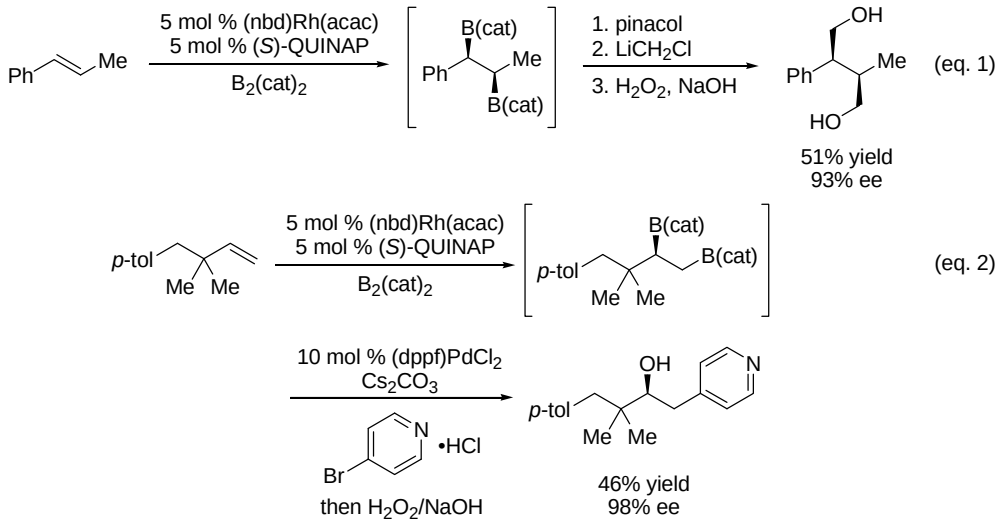
(22) (*a*) Ramirez, J.; Corberan, R.; Sanau, M.; Peris, E.; Fernandez, E. *Chem. Commun.* **2005**, 3056. (*b*) Corberan, R.; Ramirez, J.; Poyatos, M.; Peris, E.; Fernandez, E. *Tetrahedron: Asymmetry* **2006**, *17*, 1759. (*c*) Lillo, V.; Mata, J.; Ramirez, J.; Peris, E.; Fernandez, E. *Organometallics* **2006**, *25*, 5829.

alkenes. However, when chiral NHC ligands were employed with these metals, the enantioselectivities of the 1,2-bis(boronate)esters were very low (4-17% ee).

The synthetic utility of the organoboron intermediate is broad. The functionalization of this reactive intermediate allows access to connectivities not previously available by traditional organic synthesis. While several methods exist to synthesize chiral *syn*-1,2-diols, the ability to access a chiral *syn*-1,4-diol or to convert a simple alkene to an aryl alcohol in one step is challenging. The experiments in Scheme 1.7 show how diboration can provide a solution. Rhodium-catalyzed diboration of β-methyl styrene delivered the intermediate *syn*-1,2-bis(boronate)ester.[19] Exchange of the catechol group on boron for pinacol, followed by Matteson homologation and oxidation delivered the *syn*-1,4-diol in a one pot process (Scheme 1.7, eq. 1). The 1,2-bis(boronate)ester intermediate may also undergo selective cross-coupling to the primary carbon-boron bond (Scheme 1.7, eq. 2).[23] Following treatment with alkaline hydrogen peroxide, the chiral secondary alcohol is obtained in 98% ee.

(23) Miller, S. P.; Morgan, J. B.; Nepveux, F. J., V; Morken, J. P. *Org. Lett.* **2006**, *6*, 131.

Scheme 1.7. Rh(I)-Catalyzed Enantioselective Diboration/Suzuki Cross-Coupling

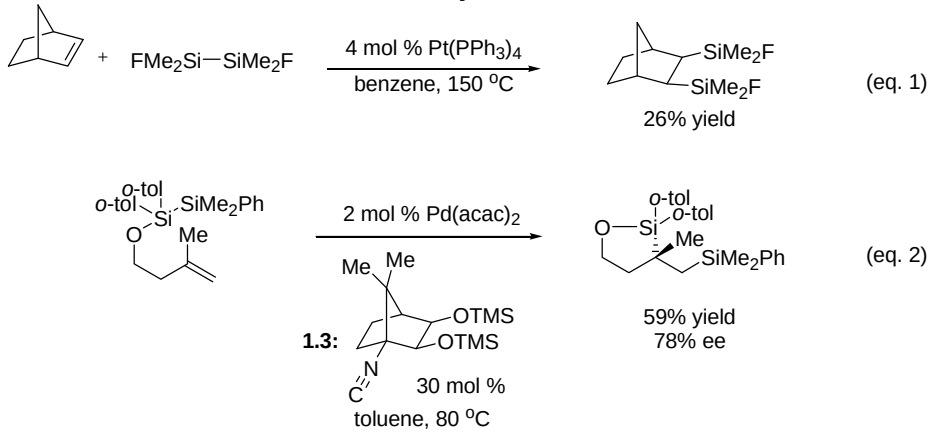


1.3.2. Disilylation of Alkenes. In 1990, Tanaka reported the first example of a transition-metal-catalyzed disilylation of olefins.[24] Previous reports illustrated that the disilylation of alkynes[25] and dienes[26] was possible; however, until Tanaka's report, the bis(silylation) of olefins was uncharted chemistry. Employing disilylation reagents bearing electronegative atoms, the platinum-catalyzed *cis*-addition of $FMe_2SiSiMe_2F$ to norborene proceeded in 26% yield (Scheme 1.8, eq. 1). However, disilylation of norborene with $PhMe_2SiSiPhMe_2$ did not proceed under analogous reaction conditions, thus illustrating that an electron-withdrawing substitutent on silicon is required. Electron-rich phosphines, thought to increase electron-density at the catalyst center, facilitated oxidative addition and enabled the reaction in higher yields.[24] While the asymmetric intermolecular bis(silylation) of olefins has yet to be reported, one might

(24) Hayashi, T.; Kobayashi, T. -A.; Kawamoto, A. M.; Yamashita, H.; Tanaka, M. *Organometallics* **1990**, *9*, 280.
(25) (*a*) Suginome, M.; Oike, H.; Park, S. –S.; Ito, Y. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 289. (*b*) Suginome, M.; Ito, Y. *J. Organomet. Chem.* **2003**, *685*, 218.
(26) Okinoshima, H.; Yamamoto, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 9263.

envision the possibility of asymmetric induction by the addition of electron-rich chiral phosphine ligands to platinum.

Scheme 1.8. Inter- and Intramolecular Disilylation of Alkenes



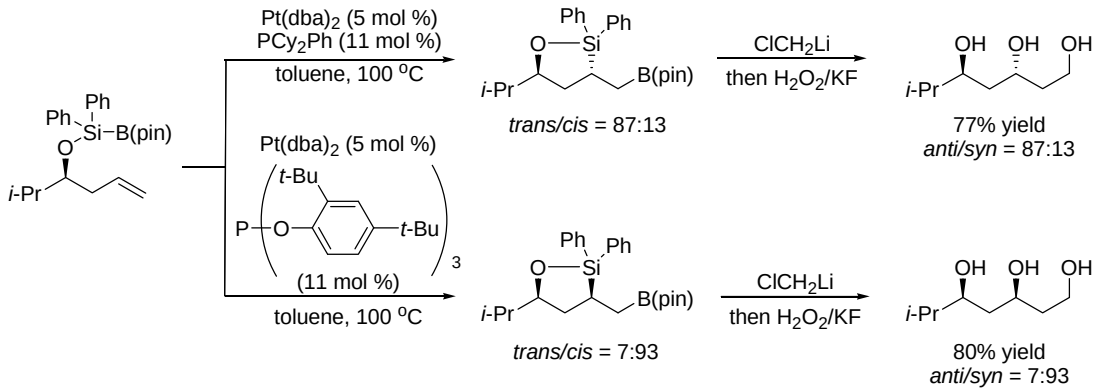
Suginome and Ito have reported the possibility of an intramolecular palladium(II)-catalyzed alkene disilylation employing *t*-butyl isocyanide ligands.[27] The *t*-alkyl isocyanide ligands render a more electron-rich palladium(II) catalyst which may be isoelectronic with Pd(0), and capable of forming the bis(silyl)palladium(II). When sterically encumbered phosphine ligands are employed on the transition-metal catalyst, the propensity for oxidative addition of disilanes to the metal is curtailed. When the isocyanide ligand is used in conjunction with palladium, the steric encumbrance around the metal center is removed, facilitating oxidative addition. Suginome and Ito have recently reported an asymmetric variant, employing chiral isocyanide **1.3** for the intramolecular disilylation of a 1,1'-disubstituted alkene (Scheme 1.8, eq. 2).[28]

(27) (*a*) Suginome, M.; Oike, H.; Park, S. -S.; Ito, Y. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 289. (*b*) Ito, Y.; Suginome, M. *Pure Appl. Chem.* **1996**, *68*, 505. (*c*) Suginome, M.; Iwanami, T.; Ohmori, Y.; Matsumoto, A.; Ito, Y. *Chem. Eur. J.* **2005**, *11*, 2954.
(28) Suginome, M.; Nakamura, H.; Ito, Y. *Tetrahedron Lett.* **1997**, *38*, 555.

1.3.3. Silylboration of Alkenes. The transition-metal-catalyzed silylboration of unfunctionalized alkenes allows for discriminatory functionalization of each olefinic carbon. In 1997, Ito and co-workers reported the first example of the silylboration of unfunctionalized alkenes.[29] The platinum-catalyzed process employed the heterometallic reagent $PhMe_2SiB(pin)$ with good regiocontrol, and yielded 2-boryl-1-silylalkanes. While the enantioselective silylboration of alkenes has yet to be reported, Suginome et al. have disclosed a diastereoselective intramolecular silylboration of alkenes (Scheme 1.9).[30] The intramolecularity minimizes formation of 1-boryl-1-silylalkanes, common by-products in the intermolecular version. Furthermore, the addition of a silicon-tether to the aliphatic alkene delivers the silylborane in a stereo- and regioselective manner. Depending on the ligand for this platinum-catalyzed process, the *cis*- or *trans*-diastereomer may be formed preferentially. Matteson homologation of the resulting silylboron followed by a Tamao-Fleming oxidation furnishes 1,3,5-triols, which are obtained in high yields.

(29) Suginome, M.; Nakamura, H.; Ito, Y. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2516.
(30) Ohmura, T.; Furukawa, H.; Suginome, M. *J. Am. Chem. Soc.* **2006**, *128*, 13366.

Scheme 1.9. Intramolecular Diastereoselective Disilylation of Alkenes



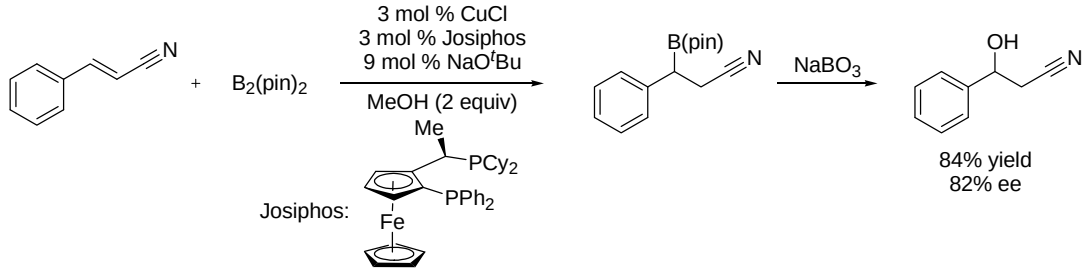
1.4. α,β-Unsaturated Ketones and Derivatives

1.4.1. Diboration of Enones. Transition-metal-catalyzed diboration of α,β-unsaturated ketones, nitriles, esters, and phosphonates generally affords the 1,4-diboration product, although the 3,4-diboration product has been observed.[31] Platinum and rhodium catalysts[32] have been effective in promoting the addition of diboron reagents to α,β-unsaturated ketones, esters, and nitriles; however, the reaction with these catalysts has yet to be rendered enantioselective. The copper-catalyzed borylation of α,β-unsaturated ketones and derivatives has recently become of interest to several research groups.[33] Transmetalation between diboron reagents and copper(I) salts produces a copper-boryl nucleophile that behaves similarly to other organocopper nucleophiles. The copper-boryl nucleophile is capable of conjugate addition to α,β-unsaturated carbonyl

(31) (*a*) Bell, N. J.; Cox, A. J.; Cameron, N. R.; Evans, J. S. O.; Marder, T. B.; Duin, M. A.; Elsevier, C. J.; Baucherel, X.; Tulloch, A. A. D.; Tooze, R. P. *Chem. Commun.* **2004**, 1854. (*b*) Lawson, Y. G.; Lesley, M. J. G.; Norman, N. C.; Rice, C. R.; Marder, T. B. *Chem. Commun.* **1997**, 2051.
(32) Kabalka, G. W.; Das, B. C.; Das, S. *Tetrahedron Lett.* **2002**, *43*, 2323.
(33) (*a*) Takahashi, K.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, 982. (*b*) Ito, H.; Yamanaka, H.; Tateiwa, J.; Hosomi, A. *Tetrahedron Lett.* **2000**, *47*, 6821. (*c*) Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034. (*d*) Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2001**, *625*, 47.

derivatives, delivering a β-boryl boron enolate. Yun and co-workers have exploited this catalyst system and extended it to employ several α,β-unsaturated substrates, including esters and nitriles.[34] The addition of a chiral ligand facilitated the introduction of a β-boryl group to an α,β-unsaturated nitrile (Scheme 1.10). Oxidation of the resulting carbon-boron bond delivered the β-hydroxy nitrile in 82% ee. Interestingly, effective catalysis required the addition of methanol to facilitate protolytic turnover of an intermediate copper enolate (see cycle C, Scheme 1.4).

Scheme 1.10. Copper-Catalyzed Enantioselective Diboration of an α,β-Unsaturated Nitrile

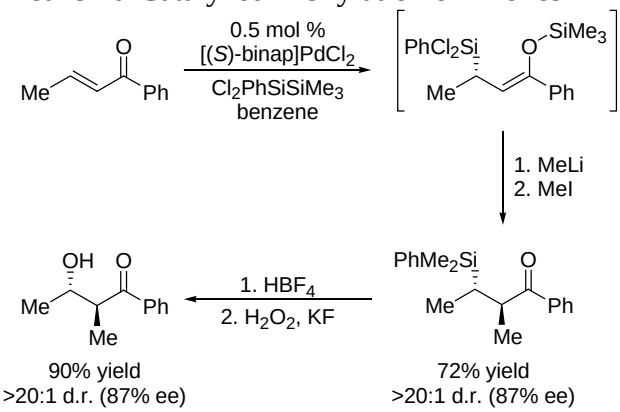


1.4.2. Disilylation of Enones. In 1998, the asymmetric disilylation of enones was developed by Hayashi and Ito.[35] While the disilylation of enones has been accomplished with Cu(I)-phosphine[36] and Pd(0) catalyst systems,[37] only the Pd(0)-phosphine catalyst reported by Hayashi and Ito renders this transformation enantioselective.[34] In the presence of BINAP, the palladium-catalyzed disilylation of 1-phenyl-2-buten-1-one with

(34) Mun, S.; Lee, J. -E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887.
(35) (*a*) Hayashi, T.; Matsumoto, Y.; Ito, Y. *Tetrahedron Lett.* **1988**, *29*, 4147; (b) Matsumoto, Y.; Hayashi, T.; Ito, Y. *Tetrahedron* **1994**, *50*, 335. (*c*) Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 5579.
(36) (*a*) Ito, H.; Ishizuka, T.; Tateiwa, J.; Sonoda, M.; Hosomi, A. *J. Am. Chem. Soc.* **1998**, *120*, 11196. (*b*) Clark, C. T.; Lake, J. F.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 84.
(37) Ogoshi, S.; Tomiyasu, T.; Morita, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2002**, *124*, 11598.

$Cl_2PhSiSiMe_3$ occurred in an enantioselective fashion (Scheme 1.11). Treatment of the 1,4-disilyl intermediate with methyl lithium, followed by alkylation with methyl iodide, produced the *anti*-α-methyl-β-silyl ketone in high diastereoselectivity. The stereochemical outcome for the alkylation of the β-silyl lithium enolate has previously been rationalized by Fleming et al., and it is such that the methyl is *anti* to the large silicon group.[38]

Scheme 1.11. Asymmetric Pd-Catalyzed Disilylation of Enones

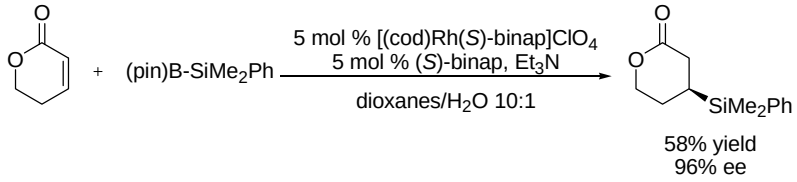


1.4.3. Silylboration of Enones. The asymmetric Rh-catalyzed addition of silylboron reagents was recently reported by Oestreich (Scheme 1.12).[39] The installation of a β-silyl moiety proceeds with acyclic as well as cyclic substrates. Excess ligand is required in order to obtain the product in high enantiomeric excess, suggesting that a high background reaction by ligand-free rhodium may occur. An additional base is also required for this transformation to proceed with high enantioselectivity. Considering that

(38) (*a*) Bernhard, W.; Fleming, I.; Waterson, D. *J. Chem. Soc., Chem. Commun.* **1984**, 28. (*b*) Bernhard, W.; Fleming, I. *J. Organomet. Chem.* **1984**, *271*, 281. (*c*) Fleming, I.; Hill, J. H. M.; Parker, D.; Waterson, D. *J. Chem. Soc., Chem. Commun.* **1985**, 318.
(39) (*a*) Walter, C.; Auer, G.; Oestreich, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5675. (b) Walter, C.; Oestreich, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 3818.

the reaction is catalyzed by rhodium(I) salts in the presence of both base and water, suggests that the mechanism is similar to that proposed by Hayashi et al. for the rhodium-catalyzed conjugate addition reaction (see Cycle C).[40]

Scheme 1.12. Enantioselective Silylboration of Enones

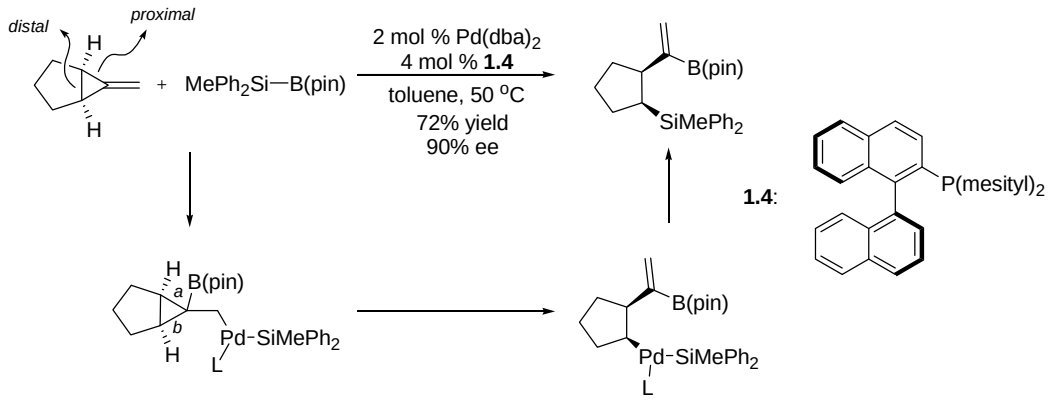


1.5. Methylenecyclopropanes

Methylenecyclopropanes (MCPs) offer a unique reactivity not available to other unsaturated hydrocarbons.[41] Transition-metal-catalyzed processes may occur on either the proximal or the distal bond of the MCP (Scheme 1.13). In addition, employing a heterobimetallic reagent poses regioselectivity as an additional challenge, which needs to be addressed in the development of such processes. Miyaura has reported the platinum-catalyzed addition of diboron reagents to the proximal bond of the methylenecyclopropanes (MCP); however, this reaction has yet to be rendered enantioselective.[42]

(40) (*a*) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052. (*b*) Review: Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.
(41) For a review on transition-metal-catalyzed reactions of MCPs: Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111.
(42) Ishiyama, T.; Momota, S.; Miyaura, N. *Synlett* **1999**, 1790.

Scheme 1.13. Pd-Catalyzed Asymmetric Silylboration of MCPs



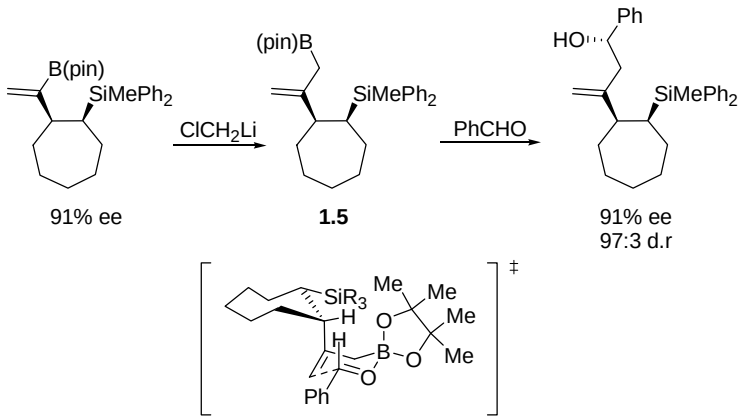
Suginome has recently reported the platinum-catalyzed silylboration of the exocyclic olefin of the MCPs, delivering boron to the more substituted carbon (Scheme 1.13). [43] The stereochemistry-determining step is the desymmetrizing carbon-carbon bond cleavage, where either bond *a* or bond *b* ruptures, dictating the configuration of the product enantiomer. The chiral ligand may have an effect on the desymmertization reaction and a number of chiral monodentate phosphines and phorphoramidite structures were examined. With the chiral ligand **1.4**, the silylboration of 6-methylenebicyclo[3.1.0]hexane proceeded to deliver the product in 90% ee.

The products resulting from the silylboration of MCPs may be further functionalized. Matteson homologation of the boronic ester with (chloromethyl)lithium occurs without interference from the silicon functional group, to deliver allyl boronic ester **1.5** (Scheme 1.14). Diastereoselective aldehyde allylation with allyl boronic ester **1.5** occurs to deliver the homoallylic alcohol in high selectivity. Stereochemical

(43) For racemic Pd- and Pt-catalyzed silylboration of MCP see: Suginome, M.; Matsuda, T.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11015. For enantioselective silylboration of MCP see: Ohmura, T.; Taniguchi, H.; Kondo, Y.; Suginome, M. *J. Am. Chem. Soc.* **2007**, *129*, 3518.

induction in the allylation reaction appears to come from a transition structure similar to that depicted in Scheme 1.14. The allylic hydrogen attached to the cycloheptane ring is oriented toward the apical boronic ester, while the large silicon group is directed away from the cyclic transition state, and the medium-sized CH_2 group is directed toward the reacting aldehyde.

Scheme 1.14. Functionalization of Silylboron Products



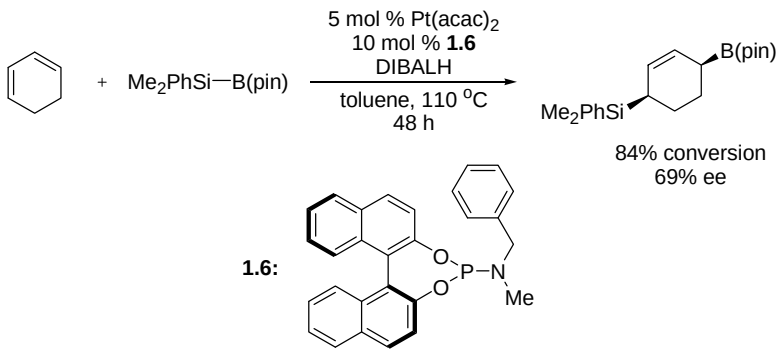
1.6. Dienes

Although many studies have been carried out on the non-enantioselective addition of diboron reagents to dienes,[44] the asymmetric variant has not been realized. While one might imagine that chirality transfer from chiral diboron reagents could be an effective tool in delivering enantiomerically enriched bis(allylic)boronate esters, this strategy does not provide high levels of selectivity.[45] For instance, the diboration of unactivated 1,3-dienes with tartrate-derived chiral diboron reagents affords 1,4-bis(boronate)esters in

(44) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun.* **1996**, 2073.
(45) Clegg, W.; Johann, T. R. F.; Marder, T. B.; Norman, N. C.; Orpen, A. G.; Peakman, T. M.; Quayle, M. J.; Rice, C. R.; Scott, A. J. *J. Chem. Soc., Dalton Trans.* **1998**, 1431.

20% diastereomeric excess, at best. Alternatively, asymmetric catalytic silylboration of unactivated dienes can be accomplished in much higher selectivity.[46] Unlike silylboration of simple alkenes, silylboration of dienes may be accomplished with nickel and platinum catalysis. However, optimal levels of selectivity have been obtained with platinum catalysis. As the example by Moberg and Gerdin depicts,[47] with $Pt(acac)_2$, DIBALH, and a chiral BINOL-derived phosphoramidite ligand, the silylboration of 1,3-cyclohexadiene proceeds in moderate selectivity (Scheme 1.15).

Scheme 1.15. Silylboration of 1,3-Cyclohexadiene



1.7. Allenes

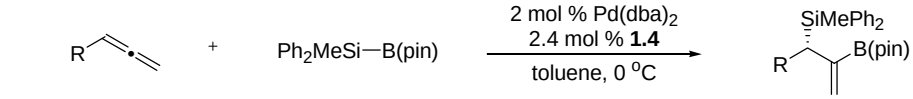
The addition of diboron reagents to allenes has been documented by Miyaura;[48] however, prior to 2004, the asymmetric diboration of allenes had yet to be reported. On the other hand, asymmetric silylboration of allenes has been well-documented.[8a, 49] Unlike with 1,3-cyclohexadiene, the silylboration of acyclic 1,2-dienes presents

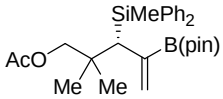
(46) (*a*) Suginome, M.; Nakamura, H.; Matsuda, T.; Ito, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4248. (*b*) Suginome, M.; Matsuda, T.; Yoshimoto, T.; Ito, Y. *Org. Lett.* **1999**, *1*, 1567. (*c*) Suginome, M.; Ito, Y. *J. Organomet. Chem.* **2003**, *680*, 43.
(47) Gerdin, M.; Moberg, C. *Adv. Synth. Catal.* **2005**, *347*, 749.
(48) Ishiyama, T.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1998**, *39*, 2357.
(49) (*a*) Suginome, M.; Ohmori, Y.; Ito, Y. *Synlett* **1999**, 1567. (*b*) Onozawa, S. -Y.; Hatanaka, Y.; Tanaka, M. *Chem. Comm*. **1999**, 1863. (*c*) Suginome, M.; Ohmori, Y.; Ito, Y. *J. Organomet. Chem.* **2000**, *611*, 403.

additional challenges: site control in the addition of the interelement reagent to the allene (2,3- *vs.* 1,2-addition) and regioselectivity (2-boryl-3-silyl *vs.* 2-silyl-3-boryl). Remarkably, Suginome and Murakami found that both of these elements can be controlled, as can the facial selectivity in these reactions. Initial studies in this area focused on the silylboration of allenes with chiral silylboron reagents and chiral catalysts.[50] In these experiments, asymmetric induction from both the catalyst and the reagent occurs to allow for facial selectivity in the silylboration of the allene. Subsequent studies by Suginome led to the development of an asymmetric silylboration reaction that employs an achiral silaboron reagent and a readily available source of palladium.[51] Silylboron Ph_2MeSi-B(pin) and $Pd(dba)_2$ work in concert with H-MOP derivative **1.4** to deliver the silylboration products in high regio- and enantioselectivities (Scheme 1.16). The highest levels of asymmetric induction occurred with allenes bearing an α-quaternary center, silylboration products were obtained in up to 93% ee.

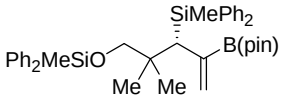
(50) (*a*) Suginome, M.; Ohmura, T.; Miyake, Y.; Mitani, S.; Ito, Y.; Murakami, M. *J. Am. Chem. Soc.* **2003**, *125*, 11174. (*b*) Ohmura, T.; Suginome, M. *Org. Lett.* **2006**, *8*, 2503.
(51) (*a*) Ohmura, T.; Taniguchi, H.; Suginome, M. *J. Am. Chem. Soc.* **2006**, *128*, 13682. (*b*) For a theoretical investigation of the mechanism for the silylboration of allenes, see: Abe, Y.; Kuramoto, K.; Ehara, M.; Nakatsuji, H.; Suginome, M.; Murakami, M.; Ito, Y. *Organometallics* **2008**, *27*, 1736.

Scheme 1.16. Enantioselective Pd-Catalyzed Silylboration of Allenes

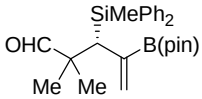




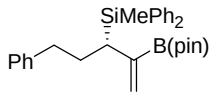
91% y, 90% ee



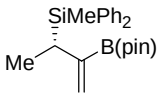
97% y, 92% ee



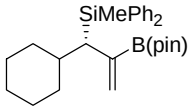
95% y, 93% ee



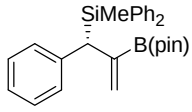
91% y, 82% ee



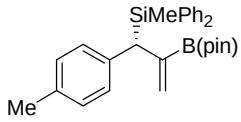
96% y, 88% ee



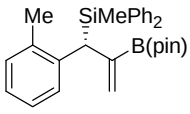
90% y, 91% ee



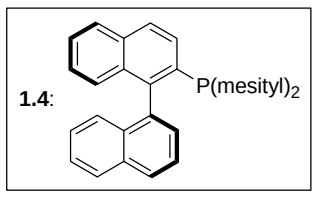
93% y, 88% ee



94% y, 89% ee



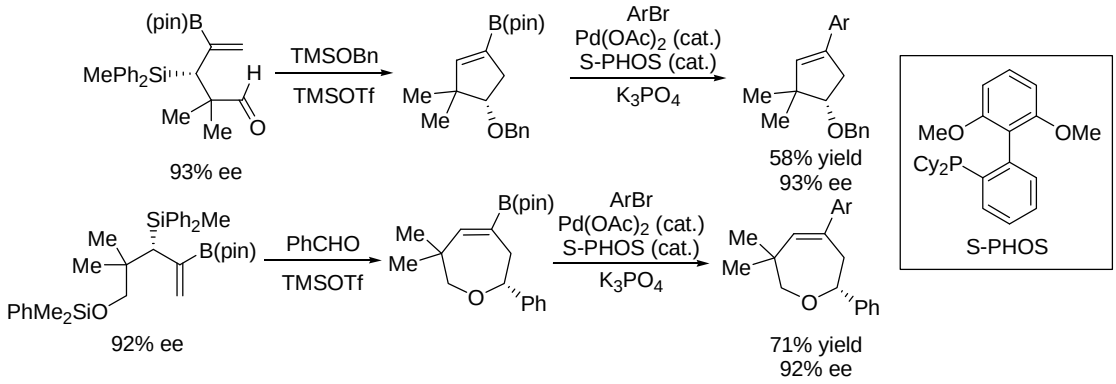
93% y, 90% ee



Suginome has developed a number of useful transformations that employ allene silylboration products. As depicted in Scheme 1.17, an intramolecular Lewis-acid catalyzed Marko-type allylation[52] with the internal aldehyde of the silylboration product occurs. This reaction proceeds with a high level of chirality transfer and furnishes a carbocyclic vinylboronate intermediate useful for cross-coupling. A related transformation is available to allenes that bear a pendant silyl ether. The addition of benzaldehyde and a Lewis acid produces cyclic ether products. These reactions also proceed with a high level of chirality transfer.

(52) (*a*) Mekhalfia, A.; Markó, I. E. *Tetrahedron Lett.* **1991**, *32*, 4779. (*b*) Mekhalfia, A.; Markó, I. E.; Adams, H. *Tetrahedron Lett.* **1991**, *32*, 4783.

Scheme 1.17. Functionalization of Silylboronate Esters



1.8. Conclusion

The catalytic addition of dimetalation reagents (diborons, disilanes, and silylborons) to unsaturated systems has been known for quite some time. It was not until recently, that reports focused on the development of the catalytic asymmetric addition of interelement reagents to π-systems. The non-enantioselective addition of diboron reagents to carbonyls and imines has also been disclosed.[53] As transition-metal-catalyzed asymmetric dimetalation continues to develop, more processes directed toward increasing the substrate scope will emerge, facilitating the rapid construction of molecularly diverse compounds. The catalytic asymmetric addition of dimetalation reagents to substrates not described here, like carbonyls and imines, will more than likely be developed. In the following two chapters, the development of the first catalytic asymmetric allene and diene diboration processes will be disclosed.

(53) Diboration of imines: (*a*) Mann, G.; John, K. D.; Baker, R. T. *Org. Lett.* **2000**, *2*, 2105. Copper-catalyzed borylation of carbonyls: (*b*) Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 11036.

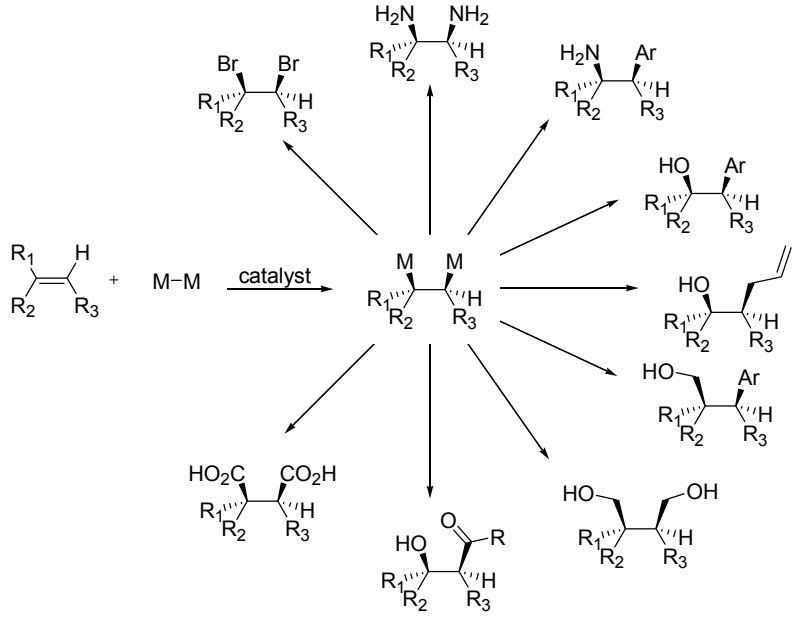
Chapter 2

Development, Scope, and Mechanism of the Palladium-Catalyzed Enantioselective Allene Diboration

2.1. Introduction

Asymmetric catalysis has redefined the field of organic chemistry over the last 40 years. In particular, metal-catalyzed transformations have revolutionized traditional organic chemistry such that previously inconceivable reactions can now be accomplished in a single step. Streamlining enantioselective small molecule synthesis would expedite discovery of biologically active compounds. Commonly in the field of asymmetric catalysis, individual methodologies are developed to address distinct transformations. In our research program, we are working to simultaneously solve many problems in asymmetric catalysis by developing catalytic asymmetric dimetalation of unsaturated substrates. These reactive intermediates might be used to target an array of unprecedented building blocks (Scheme 2.1). While previous work by the group has studied the asymmetric dimetalation of alkenes, my research has focused on allenes and, more recently, dienes (see Chapter 3).

Scheme 2.1. Dimetalation of a Single Substrate Allows for the Synthesis of Several Functionally Diverse Compounds

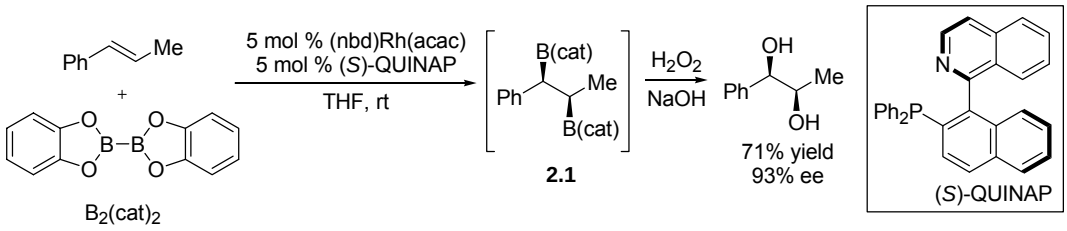


Dimetalation reactions with silylboranes, disilanes, silylgermanes, distannanes, silylstannanes, and borylstannanes have been reported.[1] However, functionalization of the silicon, tin, and germanium bond is limited to protonation and oxidation; only very specific substrates will undergo cross-coupling. *Is there an element that would undergo dimetalation and allow for further functionalization other than protonation and oxidation?* Boron is an extremely versatile element and synthetic transformations with boron are not limited to protonation and oxidation.[2] Cross-coupling, homologation, amination, and carbonylation are just a few reactions in which boron may participate. The addition of diboron reagents to alkynes was reported initially by Suzuki and Miyaura,

(1) (*a*) Suginome, M.; Ito, Y. *Chem. Rev.* **2000**, *100*, 3221. (*b*) Obora, Y.; Tsuji, Y.; Kakehi, T.; Kobayashi, M.; Shinkai, Y.; Ebihara, M.; Kawamura, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 599. (*c*) Onozawa, S. Y.; Hatanaka, Y.; Choi, N.; Tanaka, M. *Organometallics* **1997**, *16*, 5389.
(2) Brown, H. C.; Singaram, B. *Pure Appl. Chem.* **1987**, *59*, 879.

and subsequently investigated by Marder, Norman, Smith, Baker, and Iverson.[3] While alkyne diboration does not afford optically enriched products, alkene diboration was spawned from these seminal studies.[4] In 2003, the Morken group reported the first asymmetric diboration of alkenes.[5] The rhodium(I)/(*S*)-QUINAP catalyst promoted the addition of $B_2(cat)_2$ to unfunctionalized *trans*-alkenes to afford 1,2-bis(boronate)esters **2.1** in high enantiomeric excess (Scheme 2.2).

Scheme 2.2. Rhodium(I)-Catalyzed Enantioselective Alkene Diboration

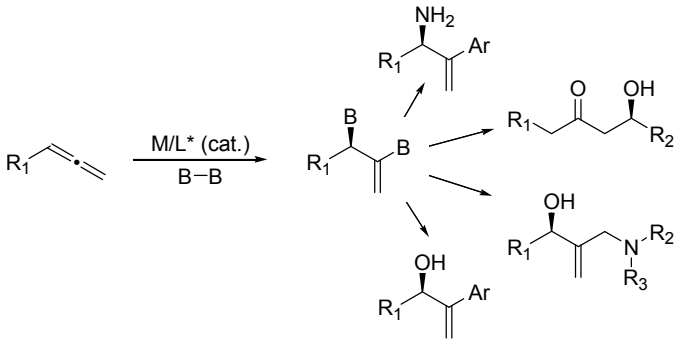


The synthetic applications of 1,2-bis(boronate)esters obtained from the enantioselective diboration of alkenes have been extensively investigated by the Morken group.[6] Alkene diboration is limited to *trans*-alkenes and monosubstituted alkenes with an α-quaternary center. The diboration of alkenes that do not fulfill these requirements proceed in low enantioselectivity. Therefore, the chiral molecular libraries built from alkene diboration are restricted to specific substrates. The extension of asymmetric

(3) (*a*) Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc.* **1993**, *115*, 11018. (*b*) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun.* **1997**, 689. (*c*) Iverson, C. N.; Smith, M. R., III, *Organometallics* **1997**, *16*, 2757. (*d*) Baker, R. T.; Nguyen, P.; Marder, T. B.; Westcott, S. A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1336. (*e*) Dai, C.; Robins, E. G.; Scott, A. J.; Clegg, W.; Yufit, D. S.; Howard, J. A. K.; Marder, T. B.; *Chem. Commun.* **1998**, 1983. (*f*) Nguyen, P.; Coapes, R. B.; Woodward, A. D.; Taylor, N. J.; Burke, J. M.; Howard, J. A. K.; Marder, T. B. *J. Organomet. Chem.* **2002**, *652*, 77.
(4) (*a*) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun.* **1997**, 689. (*b*) Iverson, C. N.; Smith, M. R., III, *Organometallics* **1997**, *16*, 2757.
(5) (*a*) Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8702. (*b*) Trudeau, S.; Morgan, J. B.; Shrestha, M.; Morken, J. P. *J. Org. Chem.* **2005**, *70*, 9538.
(6) (*a*) Miller, S. P.; Morgan, J. B.; Nepveux, F. J., V; Morken, J. P. *Org. Lett.* **2006**, *6*, 131. (*b*) Kalendra, D. M.; Duenes, R. A.; Morken, J. P. *Synlett* **2005**, *11*, 1749.

diboration to other substrate classes would expand the synthetic scope of this methodology. In particular, the development of an asymmetric transition-metal-catalyzed allene diboration would allow access to 1,2-bis(boronate)esters that bear both an allylic and vinylic boronic ester (Scheme 2.3). The selective functionalization of the carbon-boron bonds in these 1,2-bis(boronate)esters would facilitate expeditious molecular construction to generate molecularly diverse compounds.

Scheme 2.3. Transition-Metal-Catalyzed Diboration of Allenes



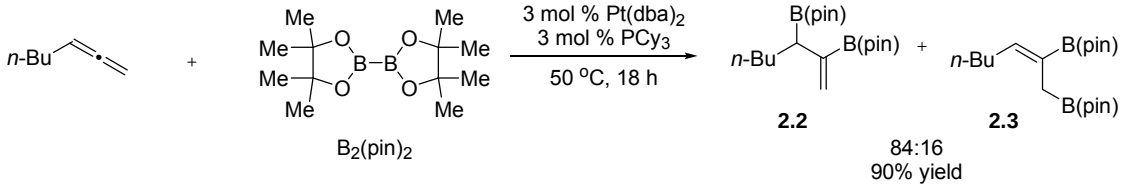
2.2. Background

The diboration of prochiral monosubstituted allenes was previously reported by Miyaura. [7] The platinum-catalyzed process delivered both regioisomeric 1,2-bis(boronate)esters **2.2** and **2.3** in high yield (Scheme 2.4). Two catalysts were investigated, $Pt(dba)_2/PCy_3$ and $Pt(PPh_3)_4$, and the regioselectivity was chiefly similar between the two. Diboration of the internal bond of the allene to form **2.2** was preferred for most substrates examined. Disparities between the two catalysts arose with a few substrates; for example, preferential diboration of the internal bond of phenyl allene

(7) Ishiyama, T.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1998**, *39*, 2357.

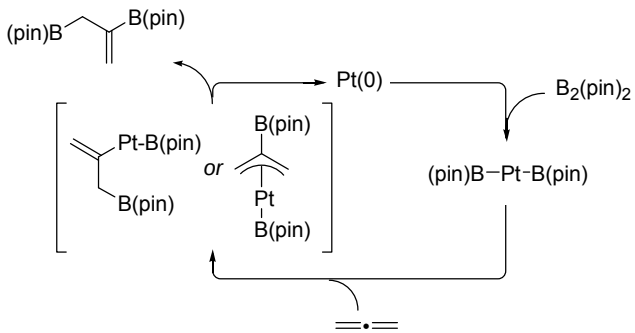
occurred with $Pt(PPh_3)_4$, while the regioselectivity was reversed when the $Pt(dba)_2/PCy_3$ catalyst system was used.

Scheme 2.4. Platinum-Catalyzed Diboration of Allenes



The proposed catalytic cycle for the platinum-catalyzed allene diboration begins with oxidative addition of the diboron reagent to the metal (Scheme 2.5). Substrate coordination and insertion allows access to a vinyl-platinum or a π-allyl intermediate. Reductive elimination from either of these intermediates affords the 1,2-bis(boronate)ester.

Scheme 2.5. Mechanism for the Pt-Catalyzed Allene Diboration

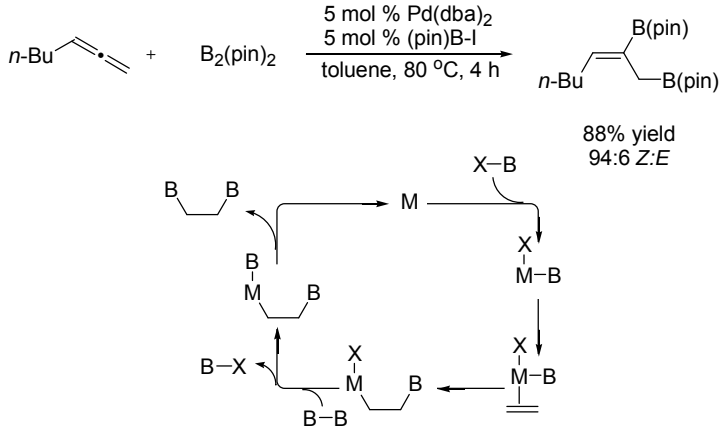


In 2001, a palladium-catalyzed diboration of allenes was reported by Cheng and co-workers (Scheme 2.6).[8] This diboration reaction does not rely on oxidative addition

(8) Yang, F. -Y.; Cheng, C. -H. *J. Am. Chem. Soc.* **2001**, *123*, 761.

of the diboron reagent to palladium; instead, Pd-catalyzed oxidative addition of a boron-halide occurred. The catalytic cycle continued by substrate insertion into the oxidative addition adduct, followed by transmetalation with the diboron reagent. Reductive elimination released the product from the catalytic cycle, regenerating the zero-valent metal catalyst, which was primed to re-enter the catalytic cycle.

Scheme 2.6. Pd-Catalyzed Diboration of Allenes Initiated by (pin)B-I



Despite these seminal findings, the development of an asymmetric allene diboration had yet to be reported. Asymmetric induction with platinum-catalysis was expected to be quite challenging due to an apparent background reaction with the phosphine-free catalyst.[4b] While one might consider replacing platinum with palladium in the reaction reported by Miyaura (Scheme 2.4), there is only one example of a Pd-catalyzed diboration that relied on oxidative addition of the diboron reagent to the metal, and it proceeded in a very low yield.[9] To provide insight into the limited examples of palladium-catalyzed diborations that hinge on oxidative addition of diboron reagents,

(9) Ishiyama, T.; Matsuda, N.; Murata, M.; Ozawa, F.; Suzuki, A.; Miyaura, N. *Organometallics* **1996**, *15*, 713.

theoretical calculations were conducted by Morokuma on the diboration of an alkyne.[10] DFT calculations were performed on the platinum- and palladium-catalyzed diboration cycles. Morokuma found that the barrier for the oxidative addition of $B_2(pin)_2$ to Pd(0) was lower in energy (9.2 kcal/mol) when compared to platinum (13.3 kcal/mol); but, the Pd-bis(boryl) adduct was less stable than the platinum analog. Overall, the oxidative addition of the diboron to palladium was endothermic, however, the same step was exothermic for platinum. Since the Pd(II)-bis(boryl) intermediate was higher in energy than the Pt(II) intermediate, most of the reaction profile for palladium was higher in energy. Based on these findings, we believed a palladium-catalyzed process could operate if the electron-density at the metal-center was increased. While a more electron-rich metal center might benefit a more favorable oxidative addition, the small barrier for reductive elimination might be enhanced.

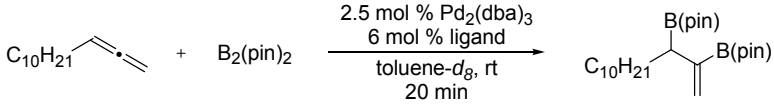
2.3. Results and Discussion

2.3.1. Development. In preliminary studies, we considered that the addition of Lewis basic phosphine ligands to a transition-metal catalyst should increase electron-density at the metal center, promoting oxidative addition of the diboron reagent to the metal and thereby facilitating the transition-metal-catalyzed reaction.[11] To test this idea, a variety of phosphine ligands were surveyed in the diboration of decyl allene with commercially available $Pd_2(dba)_3$ (Table 2.1). The reaction progress was measured by ^1H

(10) (*a*) Cui, Q.; Musaev, D. G.; Morokuma, K. *Organometallics* **1998**, *17*, 742. (*b*) Sakaki, S.; Kikuno, T. *Inorg. Chem.* **1997**, *36*, 226.
(11) (*a*) Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem. Int. Ed.* **2003**, *42*, 5749. (*b*) Amatore, C.; Jutand, A.; Meyer, G. *Inorg. Chim. Acta* **1998**, *273*, 76. (*c*) Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1655. (*d*) Segelstein, B. E.; Butler, T. W.; Chenard, B. L. *J. Org. Chem.* **1995**, *60*, 12.

NMR at a time point of 20 min. The Pd-catalyzed diboration with electron-rich phosphines delivered the desired 1,2-bis(boronate)ester in complete or nearly complete conversion (entries 3-5). Notably, the 1,2-bis(boronate)ester resulting from the addition of the diboron reagent to the internal bond of the allene was the only regioisomer of product obtained. The formation of the desired bis(boronate)ester with hexamethylphosphorus triamide and triethylphosphite was particularly encouraging, since a large number of chiral phosphorus ligands with similar electronic properties are available.

Table 2.1. Pd-Catalyzed Allene Diboration Ligand Screen[b]



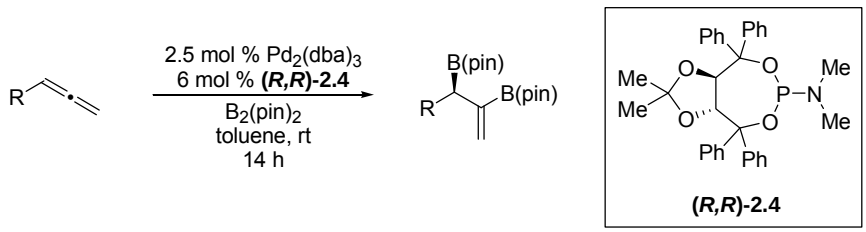
entry	ligand	% conversion[a]
1	none	0
2	P(*t*-Bu)$_3$	0
3	PCy$_3$	100
4	P(NMe$_2$)$_3$	100
5	P(OEt)$_3$	80
6	PPh$_3$	<3
7	P(OPh)$_3$	<3
8	dppe	4

[a] Determined by ^{1}H NMR Spectroscopy. [b] Reaction conditions: [allene] = 0.15 M and 1.5 equiv $B_2(pin)_2$

With effective achiral ligands identified, chiral ligands with heteroatoms bound to phosphorus were investigated to determine their ability to promote an enantioselective palladium-catalyzed allene diboration reaction. TADDOL-derived phosphoramidite **(*R*,*R*)-2.4**, in concert with $Pd_2(dba)_3$, delivered the desired 1,2-bis(boronate)ester in high

enantioselectivities (Table 2.2). [12] With this ligand, a number of prochiral monosubstituted allenes were examined, including aliphatic, aromatic and those containing oxygen. Enantioselectivities remain in the upper eighties to low nineties for all substrates investigated under these reaction conditions.

Table 2.2. Asymmetric Palladium-Catalyzed Allene Diboration



entry	R	% yield[a]	% ee[b]
1	decyl	61	91
2	cyclohexyl	62	89
3	$PhCH_2CH_2$	73	90
4	Bn	65	90
5	CH_3	68	92
6	Ph	75	87
7	^{t}Bu	42	89
8	$BnOCH_2CH_2$	57	91

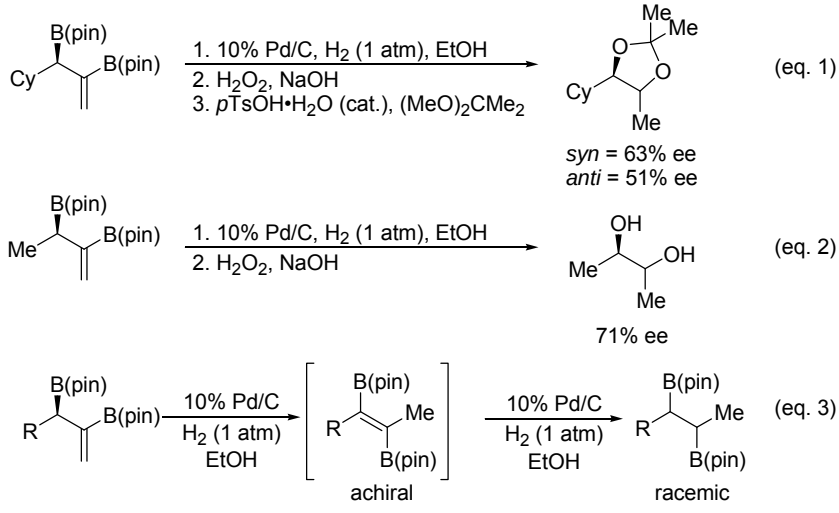
[a] Isolated yield of diboron adduct after silica gel chromatography. Average of two experiments with a difference in yield of <10% in each case. [b] Enantiomeric excess determined by chiral GLC or SFC analysis of diol obtained from diimide reduction of the vinyl boronate followed by oxidation (NaOH, H_2O_2) of the resulting saturated 2,3-bis(boronate)ester. The absolute configuration of each product was determined by comparing the derived 2,3-diol to authentic enantiomers.

Initially, enantioselectivities of the 1,2-bis(boronate)esters were determined through heterogeneous transition-metal-catalyzed hydrogenation of the vinyl boronate with palladium on carbon followed by alkaline peroxide oxidation of the resulting 1,2-bis(boronate)ester (Scheme 2.7). GLC analysis of the resulting *syn*- and *anti*-

(12) Pelz, N. F.; Woodward, A. R.; Burks, H. E.; Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 16328

diastereomeric alcohols (or the derived acetonides) revealed different enantiopurities for each diastereomer (Scheme 2.7, eq. 1 and 2). The large discrepancy in the enantiopurities between the *syn*- and *anti*-diastereomers for the cyclohexyl-2,3-diol, led us to question the accuracy of the analysis procedure. Alkene isomerization is more prevalent with palladium than with any other heterogeneous transition-metal catalyst.[13] If Pd-catalyzed isomerization of the alkene occurred to form an achiral intermediate, it would then be hydrogenated, and lead to an erosion of enantiopurity (eq. 3).

Scheme 2.7. Hydrogenation of 1,2-Bis(boronate)esters from Allene Diboration

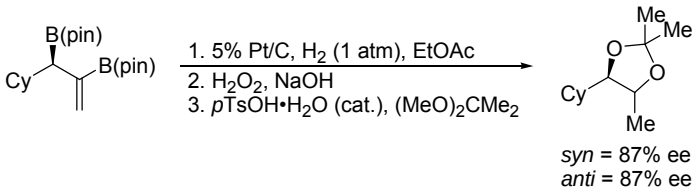


Hydrogenation with platinum on carbon afforded a diastereomeric mixture of acetonides with the same, albeit higher, levels of enantioselectivity after oxidation and acetonide protection (Scheme 2.8). In order to avoid the potential for any erosion of enantiopurity of the diboration products, reduction of the vinyl boronate under diimide

(13) Paul N. Rylander. Hydrogenation of Olefins. *Hydrogenation Methods*; Best Synthetic Methods; Academic Press, Inc: Orlando, Florida, 1985; 29-52.

conditions with 2-nitrobenzenesulfonylhydrazine (NBSH) was employed.[12] Reduction of the cyclohexyl-derived 1,2-bis(boronate)ester with NBSH revealed that the allene diboration proceeded in 89% ee (Table 2.2, entry 2). Therefore, a small erosion of enantiopurity of the diboration products did occur with platinum on carbon.

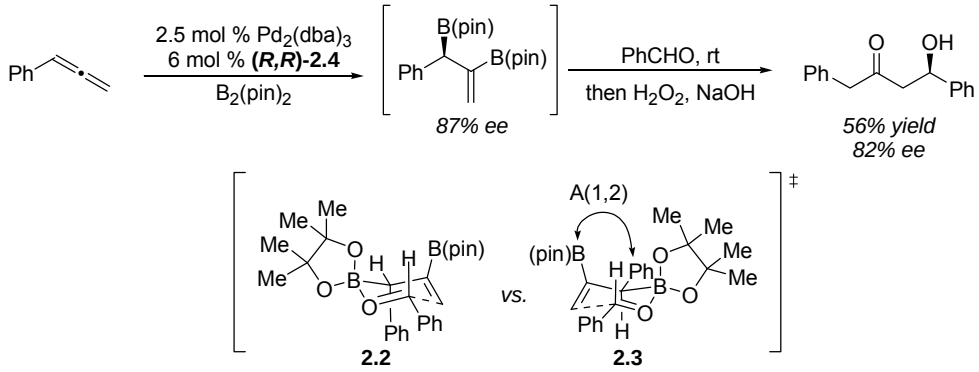
Scheme 2.8. Pt-Catalyzed Hydrogenation of the Cyclohexyl Allene Diboration Product



2.3.2. Catalyst Optimization. The α-chiral 1,2-bis(boronate)ester arising from the Pd-catalyzed allene diboration, was utilized in an aldehyde allylation reaction (Scheme 2.9). The allylation intermediate was treated with alkaline peroxide, and the β-hydroketone was obtained in 56% yield and 82% ee.[12,14] The high level of chirality transfer that occurred in the allylation sequence may be explained by two transition states, as depicted in Scheme 2.9. Axial orientation of the phenyl group on the 1,2-bis(boronate)ester in a closed transition state (**2.5**) prevents a developing A(1,2)-interaction that is present when the phenyl substituent is oriented in the equatorial position (see **2.6**). Therefore, transition state **2.5** is preferred in the allylation reaction, delivering the product with a high level of chirality transfer.

(14) The substrate scope for the aldehyde allylation of the allene diboration reaction products has been expanded, see: Woodward, A. R.; Burks, H. E.; Chan, L. M.; Morken, J. P. *Org. Lett.* **2005**, *7*, 5505.

Scheme 2.9. Aldehyde Allylation of the Allene Diboration Reaction Product



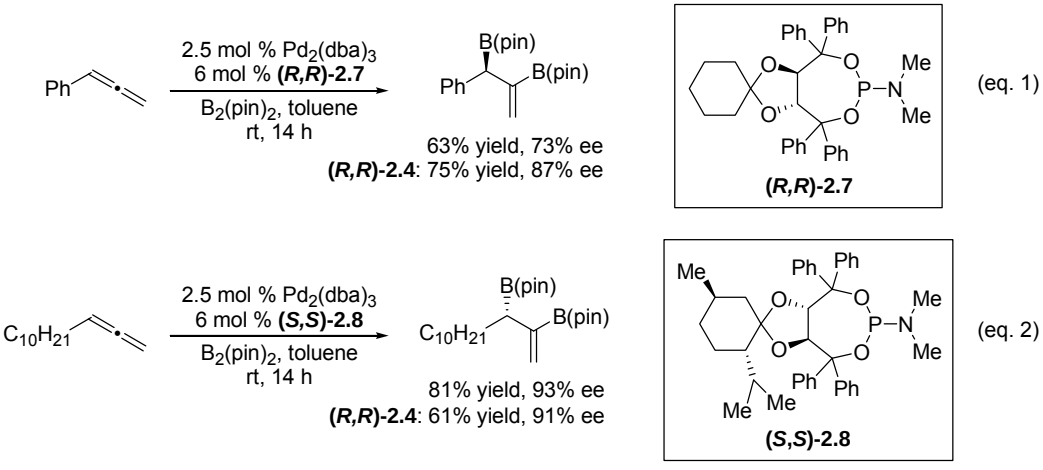
To render the 1,2-bis(boronate)esters obtained from allene diboration synthetically useful in transformations where chiralty transfer is not complete, the 1,2-bis(boronate)ester needs to be obtained in a very high enantiopurity. Therefore, structural optimization of the tunable TADDOL-derived phosphoramidite ligand scaffold was undertaken.

Palladium-catalyzed diboration of phenyl allene with the cyclohexane-derived ketal ligand **(*R*,*R*)-2.7** delivered the 1,2-bis(boronate)ester in diminished enantioselectivity (73% ee) when compared to the parent ligand **(*R*,*R*)-2.4** (Scheme 2.10, eq. 1). Diboration of decyl allene with the menthol-derived TADDOL phosphoramidite[15] **(*S*,*S*)-2.8**, inspired by Johnson et al., furnished the 1,2-bis(boronate)ester in high yield and comparable enantioselectivity (93% ee) to the parent phosphoramidite **(*R*,*R*)-2.4** (Scheme 2.10, eq. 2). The impact of the cyclohexane-derived ketal modification of the TADDOL ligand structure on the enantioselectivity of the diboration is minimal. The ketal moiety of this ligand scaffold is far removed from phosphorus; therefore, the impact

(15) We are grateful for the donation of **(*S*,*S*)-2.8**, prepared by the Johnson lab. For the preparation of the menthol-derived TADDOL please see: Nahm, M. R.; Potnick, J. R.; White, P. S.; Johnson, J. S. *J. Am. Chem. Soc.* **2006**, *128*, 2751.

of this group on the enantioselectivity may be puzzling. However, the orientation of the ketal group affects the spatial arrangement of the aryl groups on the TADDOL backbone, thereby influencing the chiral environment around phosphorus. Crystal structures of various TADDOL derivatives illustrate the conformational influence of each element of the scaffold.[16,17] In the crystal structure of (*R,R*)-TADDOLPNMe$_2$, the ketal substituent is oriented directly toward the π-system of one of the aromatic rings, increasing the steric encumbrance of the ketal moiety causes rotation of the aromatic rings in order to avoid penalizing steric interactions, subsequently altering the chiral pocket.

Scheme 2.10. Allene Diboration with Cyclohexane-Derived TADDOL Derivatives

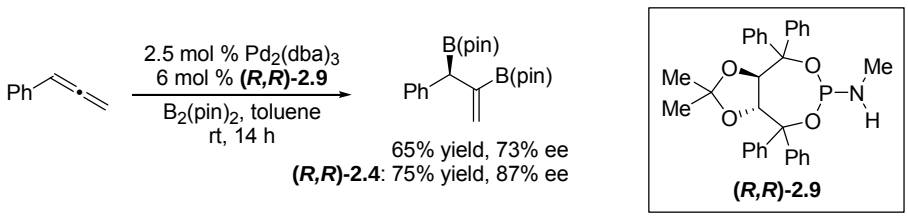


The amine moiety of the TADDOL-derived phosphoramidite ligand should have the greatest impact on enantioselectivity since it is adjacent to phosphorus, and therefore closer to palladium. Diboration of phenyl allene with the methylamine-derived

(16) (*a*) Bayer, A.; Thewalt, U.; Rieger, B. *Eur. J. Inorg. Chem.* **2002**, 199. (*b*) Bayer, A.; Murszat, P.; Thewalt, U.; Rieger, B. *Eur. J. Inorg. Chem.* **2002**, 2614.
(17) For a crystal structure of **(*R,R*)-2.4** see: Keller, E.; Maurer, J.; Naasz, R.; Schader, T.; Meetsma, A.; Feringa, B. L. *Tetrahedron: Asymmetry* **1998**, *9*, 2409. For crystal structures of TADDOL-derivatives, see: (*a*) Seebach, D.; Plattner, D. A.; Beck, A. K.; Wang, Y. M.; Hunziker, D. *Helv. Chim. Acta* **1992**, *75*, 2171. (*b*) Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 92.

phosphoramidite **(*R,R*)-2.9** delivered the 1,2-bis(boronate)ester in 73% ee (Scheme 2.11). Given that a diminished enantiomeric excess was obtained with a primary amine, it was predicted that increasing the steric encumbrance of the amine moiety should increase the enantiopurity of the product.

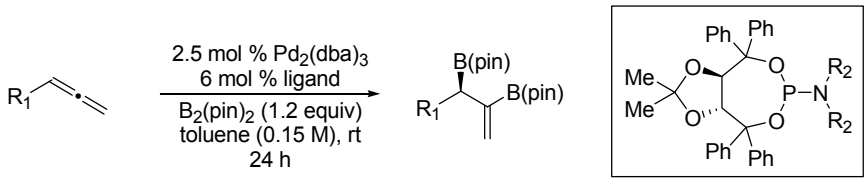
Scheme 2.11. Allene Diboration with Methylamine-Derived TADDOL Ligand

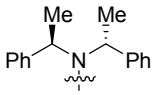


Four phosphoramidites with secondary amines were prepared and employed in diboration reactions with various allenes to survey the impact of a sterically encumbered amine on the enantioselectivity (Table 2.3).[18] All modifications of the amine moiety diminished the enantiopurity of the products. When the size of the amine was dramatically increased from dimethylamine to bis(α-methyl-benzylamine) (ligand **(*R,R*)-2.13**) diboration was inhibited. Thus, increasing or decreasing the steric encumbrance of the amine resulted in suboptimal enantioselectivities and the optimal structure appeared to be the dimethylamine derivative.

(18) Burks, H. E.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 8766.

Table 2.3. Allene Diboration with Different Amine Moieties on the TADDOL-Derived Phosphoramidite Scaffold

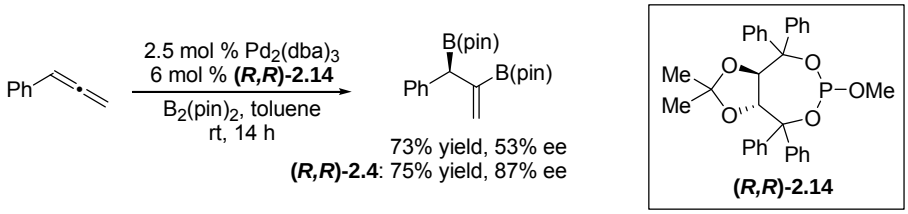


ligand	R_2	R_1 = decyl % yield[a] (% ee)	R_1 = Cy % yield[a] (% ee)	R_1 = Ph % yield[a] (% ee)
(*R,R*)-2.4	Me	61 (91)[b]	62 (89)[b]	75 (87)[b]
(*R,R*)-2.10	Et	42 (48)[b]	18 (52)	38 (30)
(*R,R*)-2.11	$(CH_2)_4$	80 (86)	80 (85)	53 (72)
(*R,R*)-2.12	$(CH_2)_5$	58 (47)	29 (46)	50 (30)
(*R,R*)-2.13		0	0	0

[a] Isolated yield determined after silica gel chromatography. Enantiomeric excess determined for the diastereomeric diols prepared by sequential diimide reduction and oxidation of the diboration product. [b] Reaction time of 12 h.

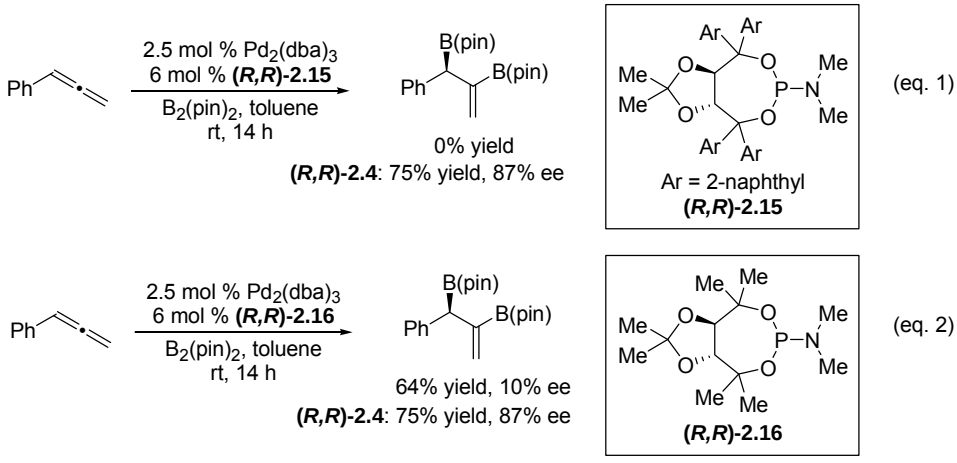
We also exchanged the amine moiety for other heteroatom functionalities and examined their impact on the enantioselectivity of the diboration. Since triethylphosphite was shown to be very effective in promoting the diboration of decyl allene (Table 2.1), a chiral version of this ligand, **(*R,R*)-2.14**, was examined. This structure was quite effective in promoting the diboration of phenyl allene, as the desired product was obtained in 73% yield (Scheme 2.12). However, the 1,2-bis(boronate)ester was obtained in a disappointing 53% ee. Based on these results, the optimal substituent attached to phosphorus, which delivered the highest enantioselectivities thus far, was dimethylamine.

Scheme 2.12. Diboration of Phenyl Allene with TADDOL-Derived Phosphite



In a further attempt to increase the level of stereoinduction for the allene diboration reaction, the modification of the aryl groups on the TADDOL-derived phosphoramidite backbone was investigated. Utilizing the 2-naphthyl-derived phosphoramidite, **(*R,R*)-2.15**, completely inhibited the diboration of phenyl allene (Scheme 2.13, eq. 1). Phosphoramidite **(*R,R*)-2.16**, which did not contain aryl groups on the backbone, promoted the diboration phenyl allene, but the 1,2-bis(boronate)ester was nearly racemic (eq. 2). Thus it appears that aryl groups on the backbone are required for high asymmetric induction; however, when the aryl groups are too sterically encumbered catalysis is inhibited.

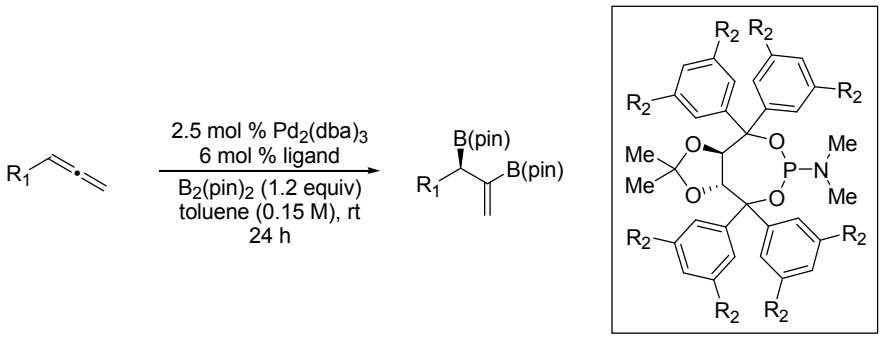
Scheme 2.13. Allene Diboration with TADDOL-Derived Phosphoramidities with Modified TADDOL Backbones



Pregosin and Albinati have demonstrated that 3,5-dialkyl-substitution of aromatic groups attached to the phosphorus of phosphine based ligands intensified the rigidity of the chiral pocket and increased enantioselectivities in Pd-catalyzed transformations.[19] In an analogous manner, TADDOL derivatives with *meta* substituted aryl groups were synthesized and surveyed in the diboration of various allenes (Table 2.4). The *meta*-xylyl substituted phosphoramidite **(*R*,*R*)-2.17** increased enantioselectivities for all substrates. The sterically encumbered 3,5-di-*tert*-butyl substituted phosphoramidite ligand **(*R*,*R*)-2.18** promoted a slower reaction in addition to delivering diminished enantioselectivities when compared to **(*R*,*R*)-2.17**. An electron-deficient TADDOL-phosphoramidite with 3,5-trifluoromethyl substituted aryl groups (ligand **(*R*,*R*)-2.19**), sterically less encumbered than **(*R*,*R*)-2.18**, curtailed product formation and enantioselectivity. Based on these results, a TADDOL derivative with electron-donating 3,5-dimethoxy aryl groups on the backbone should increase the product formation and deliver enantioselectivities comparable to **(*R*,*R*)-2.17**. Unfortunately, diboration with ligand **(*R*,*R*)-2.20** afforded the 1,2-bis(boronate)ester of decyl allene in a modest 35% yield and 60% ee. After tuning all of the elements of the TADDOL-phosphoramidite ligand scaffold, we concluded that the optimal ligand for the asymmetric palladium-catalyzed allene diboration was **(*R*,*R*)-2.17**.

(19) (*a*) Trabesinger, G.; Albinati, A.; Feiken, N.; Kunz, R. W.; Pregosin, P. S.; Tschoerner, M. *J. Am. Chem. Soc.* **1997**, *119*, 6315. (*b*) Tschoerner, M.; Pregosin, P. S.; Albinati, A. *Organometallics* **1999**, *18*, 670. (*c*) Selvakumar, K.; Valentini, M.; Pregosin, P. S.; Albinati, A.; Eisentrager, F. *Organometallics* **2000**, *19*, 1299. (*d*) Dotta, P.; Magistrato, A.; Rothlisberger, U.; Pregosin, P. S.; Albinati, A. *Organometallics* **2002**, *21*, 3033. (*e*) Dotta, P.; Kumar, P. G. A.; Pregosin, P. S.; Albinati, A.; Rizzato, S. *Organometallics* **2004**, *23*, 2295.

Table 2.4. Allene Diboration with *meta*-Substituted Aryl Groups on the TADDOL Backbone



ligand	R_2	R_1 = decyl % yield[a] (% ee)	R_1 = Cy % yield[a] (% ee)	R_1 = Ph % yield[a] (% ee)
(*R*,*R*)-2.17	Me	72 (98)[b]	92 (93)	72 (97)
(*R*,*R*)-2.18	^{t}Bu	34 (63)[b]	39 (66)	26 (51)
(*R*,*R*)-2.19	CF_3	24 (38)[b]	61 (39)	38 (36)
(*R*,*R*)-2.20	OMe	35 (60)	-	-

[a] Isolated yield determined after silica gel chromatography. Enantiomeric excess determined for the diastereomeric diols prepared by sequential diimide reduction and oxidation of the diboration product. [b] Reaction time of 12 h.

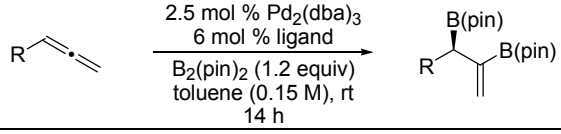
2.3.3 Substrate Scope. With the optimal ligand for the palladium-catalyzed asymmetric diboration of prochiral allenes in hand, the substrate scope was further examined (Table 2.5).[20] For the most part, aliphatic and oxygen containing allenes afforded 1,2-bis(boronate)esters in 97-98% ee (entries 1-6). As can be seen in Table 2.5, aromatic allenes also worked quite well for this transformation (entries 7-11).

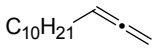
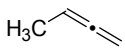
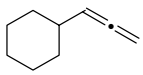
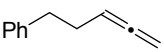
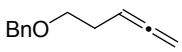
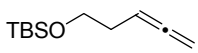
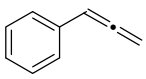
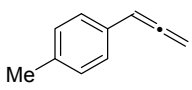
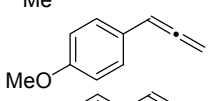
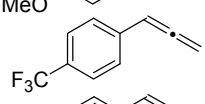
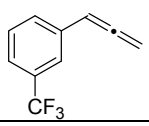
In the Pt-catalyzed allene diboration developed by Miyaura, the diboration of electron-rich allenes delivered 1,2-bis(boronate)esters **2.3**, where diboration of the terminal bond of the allene was the predominant product.[9] Accordingly, we considered that the manipulation of the electronics of phenyl allene derivates would allow for

(20) Burks, H. E., Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 8766.

regioisomeric product formation. Electron-rich and –deficient substrates were prepared and subjected to the diboration reaction conditions; all substrates afforded the desired product in high enantioselectivities (Table 2.5, entries 8-11). Diboration products which resulted from the diboration of the terminal bond of the allene were not observed for any substrate examined. Diboration of *para*-nitro substituted phenyl allene failed to deliver any products from diboration; starting material was recovered after 24 h. Despite the short comings with the *para*-nitro substituted pheny allene, a broad substrate scope exists for the Pd-catalyzed allene diboration.

Table 2.5. Substrate Scope for the Pd-Catalyzed Allene Diboration

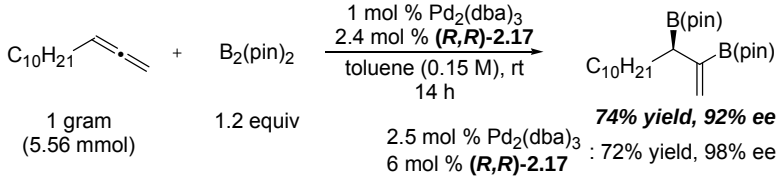


entry	substrate	ligand: ***(R,R)*-2.4**		ligand: ***(R,R)*-2.17**	
		% yield[a]	% ee[b]	% yield[a]	% ee[b]
1		61	91	72	98
2		68	92	77	95
3		62	89	92	93
4		73	90	76	97
5		57	91	85	97
6				68	97
7		75	87	71	97
8				71	95
9				68	94
10[c]				52	94
11[c]				52	90

[a] Isolated yield of purified product. [b] Enantiomeric excess determined for diastreomeric diols prepared by sequential diimide reduction and oxidation of the reaction product. [c] 0.3 M [substrate], 3 equiv of $B_2(pin)_2$, 24 h.

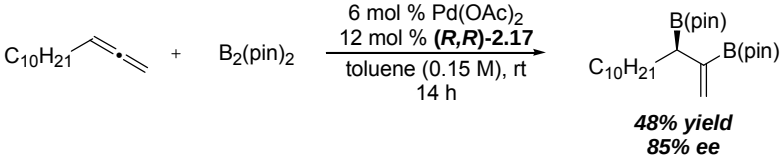
The synthetic utility of Pd-catalyzed allene diboration was further extended by performing a large scale (1 gram) diboration of decyl allene at a catalyst loading of 1 mol % $Pd_2(dba)_3$ and 2.5 mol % ***(R,R)*-2.17** (Scheme 2.14). The desired 1,2-bis(boronate)ester was obtained in 74% yield and 92% ee.[18]

Scheme 2.14. Large-Scale Allene Diboration



One might ask whether the reaction may be set up on the bench top and not in an inert atmosphere glove box. In this case, oxidation of Pd(0) will occur if precautions are not taken to exclude oxygen from reaction mixtures.[21] However, the addition of phosphine ligands to Pd(II) sources will generate Pd(0) *in situ* and Pd(II) salts are often stable in air. Palladium(II) acetate, in conjunction with ligand **(*R,R*)-2.17**, catalyzed the diboration of decyl allene to deliver the desired 1,2-bis(boronate)ester in 48% yield and 85% ee (Scheme 2.15). The yield and enantioselectivity are not as high as with $Pd_2(dba)_3$ and ligand **(*R,R*)-2.17**; however, the further optimization of reaction conditions could lead to an increase in the yield and enantioselectivity for this transformation.

Scheme 2.15. Pd(II)-Catalyzed Allene Diboration

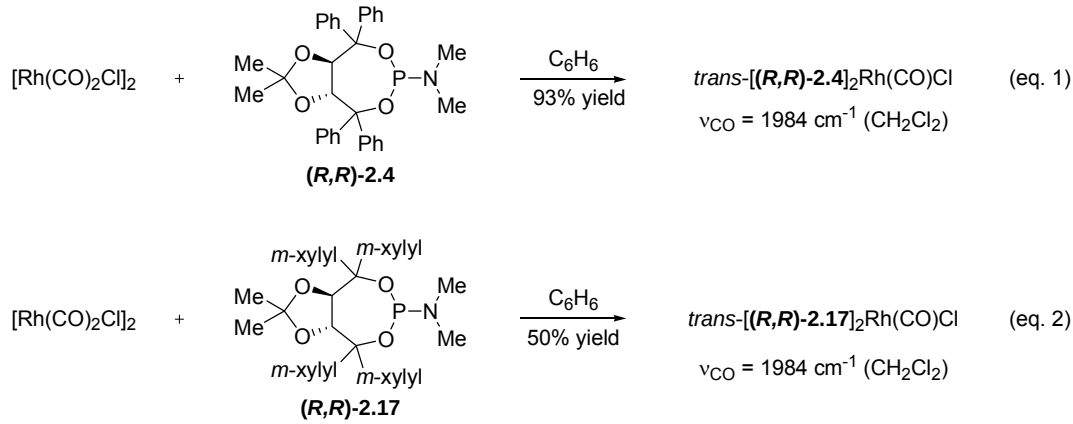


2.3.4. Mechanism. 2.3.4.1. Mechanism: Ligand Analysis. Our initial hypothesis when developing the Pd-catalyzed diboration was that the addition of electron-rich phosphine ligands would increase electron-density at palladium, promoting the oxidative

(21) Yoshida, T.; Otsuka, S. *Inorg. Syn.* **1990**, *28*, 113.

addition of the diboron reagent and stabilizing Pd(II) intermediates during the catalytic cycle. The electron-donating ability of phosphines, phosphites, and phosphorus triamides to metals has been reported;[22] but, a measure of the electron-donating ability of a TADDOL-derived phosphoramidite had yet to be reported. Generally, the electron-donating ability of a phosphine may be measured by the CO stretching frequency of the derived *trans*-$L_2Rh(CO)Cl$ complexes.[23] Therefore, rhodium-complexes containing TADDOL-derived phosphoramidite ligands **(*R*,*R*)-2.4** and **(*R*,*R*)-2.17** were prepared from dichlorotetracarbonyldirhodium, $[Rh(CO)_2Cl]_2$ (Scheme 2.16).[24]

Scheme 2.16. Preparation of *trans*-$L_2Rh(CO)Cl$ Complexes with **(*R*,*R*)-2.4** and **(*R*,*R*)-2.17**



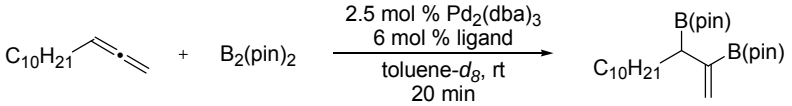
The CO stretching frequencies of the resulting rhodium-complexes were measured and found to be higher than for the triphenylphosphine derivative, suggesting that the phosphoramidite ligands are weaker donors than triphenylphosphine (Table

(22) Clarke, M. L.; Cole-Hamilton, D. J.; Slawin, A. M. Z.; Woollins, J. D. *Chem. Commun.* **2000**, 2065.
(23) (*a*) Otto, S.; Roodt, A. *Inorg. Chim. Acta* **2004**, *357*, 1. (*b*) Vastag, S.; Heil, B.; Markó, L. *J. Mol. Catal.* **1979**, *5*, 189.
(24) McCleverty, J. A.; Wilkinson, G. *Inorg. Syn.* **1966**, *8*, 214.

2.6).[18] However, the TADDOL-derived phosphoramidite ligands were more reactive than triphenylphosphine in promoting the diboration reaction. Based on the CO stretching frequency of the *trans*-$L_2RhCO(Cl)$ complex, triethylphosphite provided a higher reactivity than expected in the diboration. In the allene diboration reaction, a rough correlation exists between reactivity and the CO stretching frequency of the Rh complex. However, a better correlation appears to exist between ligand reactivity and the pK_a of the derived R_3PH^+ ion.[25] The pK_a measurement of the protonated phosphine is not sensitive to backbonding and correlates with the rate of oxidation of LPd(0) complexes to phenyl iodide.[26] The pK_a of phosphoramidites are unknown; however, experiments from Pregosin et al.[27] suggest that the binol-derived phosphoramidite may be only a slightly weaker donor than PCy_3 to a Pd(II) allyl complex. Collectively, these data suggest that the donation of electrons to Pd(II) complexes that are not inclined to back donate, is the important feature.

(25) Rahman, M. M.; Liu, H. –Y.; Eriks, K.; Prock, A.; Fiering, W. P. *Organometallics* **1989**, *8*, 1.
(26) Amatore, C.; Carré, E.; Jutland, A.; M'Barki, M. A. *Organometallics* **1995**, *14*, 1818.
(27) Filipuzzi, S.; Pregosin, P. S.; Albinati, A.; Rizzato, S. *Organometallics* **2006**, *25*, 5955.

Table 2.6. Comparison of the Lewis Basicity of Phosphorus Ligands to CO Stretching Frequencies from *trans*-$L_2Rh(CO)Cl$ Complexes



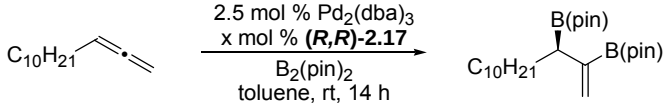
entry	ligand	% conv.[a]	ν_{CO} (cm^{-1})[b]	pK_a[c]
1	none	0		
2	P(*t*-Bu)$_3$	0		11.4
3	PCy_3	100	1943	9.7
4	$P(NMe_2)_3$	100	1964	
5	$P(OEt)_3$	80	1996	3.31
6	PPh_3	<3	1979	2.73
7	**(*R*,*R*)-2.4**	28	1984	
8	**(*R*,*R*)-2.17**	19	1984	
9	$P(OPh)_3$	<3	2016	-2.00
10	dppe	4		

[a] Determined by ^1H NMR spectroscopy. [b] Values are in CH_2Cl_2. See ref. 23 for ν_{CO} for entries 3-6, 8 and 9. See Experimentals for the determination of ν_{CO} in entries 7 and 8. Please note that entries 3 and 6 were repeated as a check for technique. [c] Values are in nitromethane. Data from ref. 25.

The asymmetric Pd-catalyzed allene diboration reaction is an example of ligand accelerated catalysis. [28] Enantioselective reactions that are governed by ligand accelerated catalysis may still operate with a high level of asymmetric induction, even when the metal-to-ligand ratio is less than one. In accord with this paradigm, high selectivities of the 1,2-bis(boronate)ester were obtained even as the ligand loading decreased (Table 2.7). Nonetheless, for optimal levels of stereoinduction, a slight excess of ligand relative to Pd is required.

(28) For a review on ligand-accelerated catalysis: Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059.

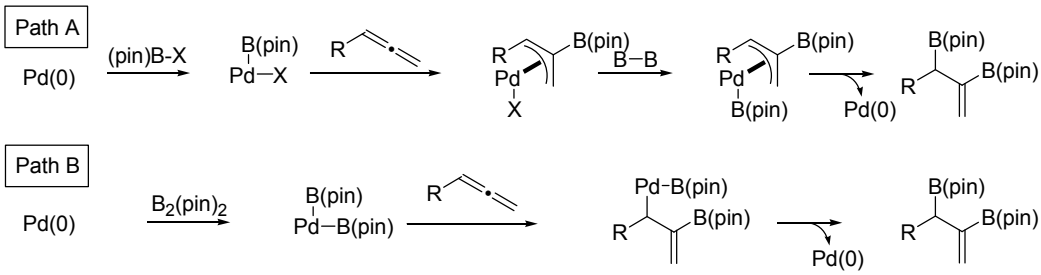
Table 2.7. Ligand Accelerated Catalysis of the Allene Diboration Reaction



entry	(*R,R*)-**2.17**/Pd	% yield	% ee
1	1.2:1	72	98
2	1.08:1	78	96
3	0.5:1	71	90
4	0.1:1	54	53
5	0	10% conv.	0

2.3.4.2. Mechanism: Crossover Experiment. There are two distinct mechanisms that may describe the diboration catalytic cycle. As previously mentioned, the first mechanism is that put forth by Cheng and co-workers and involves the oxidative addition of (pin)B-X to palladium (Scheme 2.17, path A).[8] The second mechanism involves oxidative addition of the diboron reagent to palladium (Scheme 2.17, path B). Both catalytic pathways continue to form the desired product.

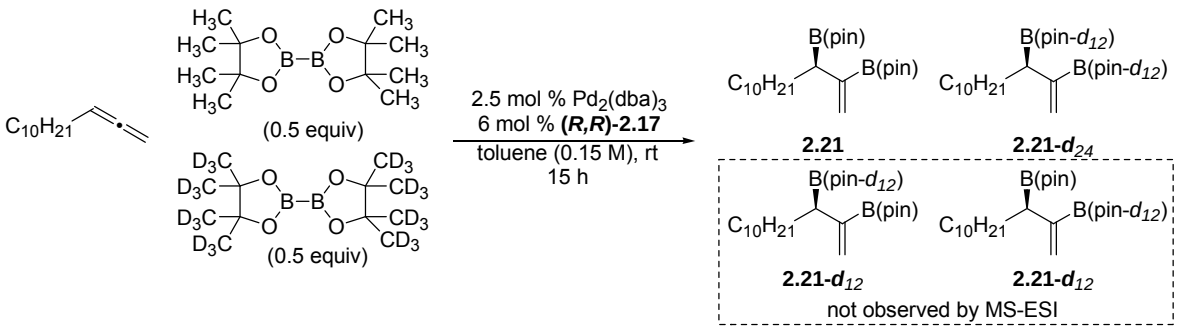
Scheme 2.17. Two Possible Pathways for the Initiation of Allene Diboration



Evidence for the oxidative addition of the diboron reagents to Pd has not been provided in the literature, and according to Morokuma, the oxidative addition of diboron reagents provides unstable Pd(II) intermediates.[10a] However, the Cheng mechanism (path A) usually gives the terminal addition product. A crossover experiment was designed in

order to learn whether oxidative addition of the diboron reagent to Pd(0) was occurring. Deuterated bis(pinacolato)diboron,[18] $B_2(pin\text{-}d_{12})_2$, was synthesized[18,29] and used in the reaction mixture along with an equal molar amount of the unlabeled $B_2(pin)_2$ (Scheme 2.18). Analysis of the unpurified reaction mixture by mass spectrometry revealed only the presence of **2.21** and **2.21-*d*$_{24}$**. Since the mechanism depicted in path A of Scheme 2.17 relies on transmetalation of the diboron reagent to afford the desired product, then 1,2-bis(boronate)esters **2.21-*d*$_{12}$**, which contain mixed pinacol groups on boron, should have been observed. Therefore, path B seems more likely.

Scheme 2.18. Crossover Experiment for Allene Diboration

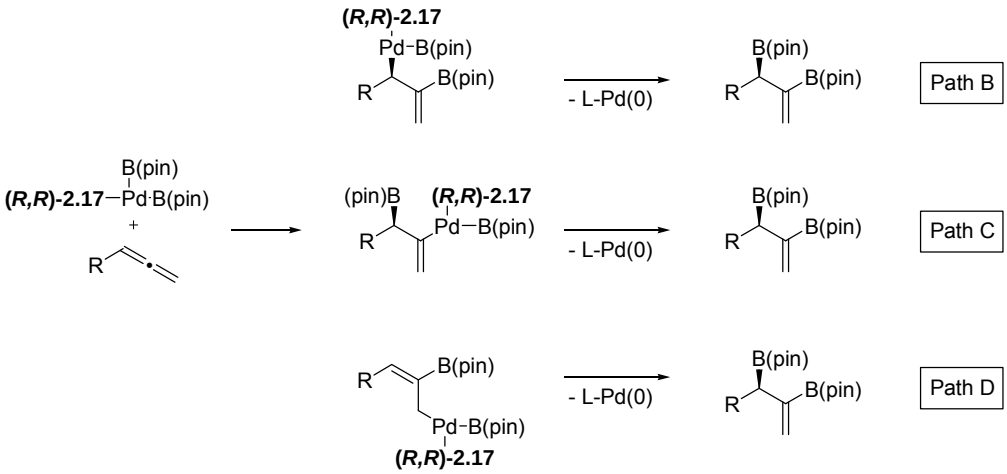


2.3.4.3. Mechanism: Diastereodifferentiation Experiment. Support for the formation of the Pd(II)-bis(boryl) intermediate resulting from the oxidative addition of $B_2(pin)_2$ to Pd was garnered from the crossover experiment. However, the mechanism for substrate insertion into the Pd(II)-intermediate could not be elucidated from this

(29) A modified procedure for the preparation of pinacol-d_{12} was taken from: Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 14263. For the preparation of $B_2(pin\text{-}d_{12})_2$ see: Ishiyama, T.; Murata, M.; Ahiko, T. -A.; Miyaura, N. *Org. Synth.* **2000**, *77*, 176.

experiment. Three pathways are conceivable for substrate insertion into the Pd(II) intermediate (Scheme 2.19). The first two pathways involve reaction by insertion of the internal bond of the allene, forming an η^1-allyl intermediate (path B) or a vinyl-Pd intermediate (path C). The final pathway differs by insertion of the terminal bond of the allene, affording a regioisomeric η^1-allyl intermediate. This path requires π-allyl isomerization and reductive elimination to yield the desired product (Scheme 2.19, path D).

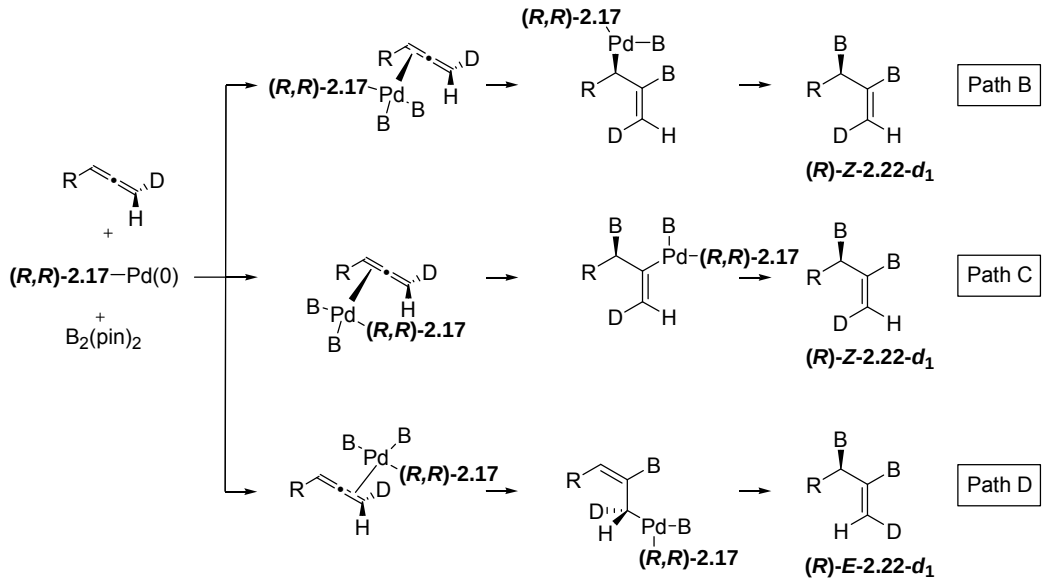
Scheme 2.19. Potential Mechanisms for Allene Insertion



A chiral labeled allene, in conjunction with a chiral catalyst to control the facial selectivity of insertion, would deliver diastereomerically different 1,2-bis(boronate)esters from the reaction paths above (Scheme 2.20). If stereoselective olefin insertion occurred with the internal bond of the allene, reductive elimination from the Pd(II) intermediates would afford a 1,2-bis(boronate)ester (**(*R*)-*Z*-2.22-*d*$_1$**) where deuterium is *trans* to boron (paths B and C). On the contrary, if substrate insertion occurred with the terminal bond

of the allene, the catalyst will control the facial selectivity of insertion, requiring that addition occur to the top-face of the allene (path D). This would afford a diastereomerically different Pd(II) intermediate; ensuing reductive elimination would provide **(*R*)-*E*-2.22-*d*$_1$**.

Scheme 2.20. Diastereodifferentiation Experiment to Determine the Mechanism of Allene Insertion

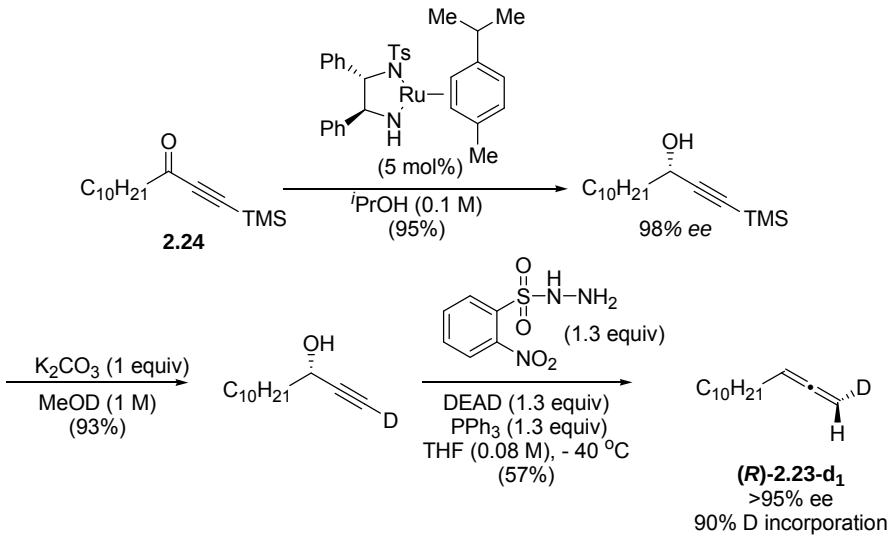


The synthesis of chiral labeled allene **(*R*)-2.23-*d*$_1$** began with trimethylsilyl-protected propargyl ketone **2.24**, which was prepared in two steps from commercially available undecanal (Scheme 2.21).[18,30] Noyori transfer hydrogenation of the propargyl ketone afforded the desired alcohol in 98% ee.[31] Deprotection of the alkyne with potassium carbonate in methanol-*d*$_1$ afforded the labeled alkyne in 93% yield. It was not

(30) Matsumara, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.
(31) Catalyst Preparation: Haack, K. -J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Eng.* **1997**, *36*, 285. Transfer Hydrogenation: Matsumara, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.

possible to completely deuterate this substrate, and a slight amount of protonated product was carried through the synthesis. The chiral labeled allene **(*R*)-2.23-*d*$_1$** was then formed under Mitsunobu reaction conditions,[32] in a procedure developed by Myers, in good yield and high enantiomeric excess.[33]

Scheme 2.21. Synthesis of Chiral Deuterated Allene **(*R*)-2.23-*d*$_1$**



The stereodifferentiating diboration of chiral labeled allene **(*R*)-2.23-*d*$_1$** was conducted with the chiral catalyst prepared from ligand **(*R,R*)-2.17**; the reaction was monitored by ^{1}H NMR (Figure 2.1).[18] The chemical shift assignments of the product were made by NOESY analysis of the unlabeled reference 1,2-bis(boronate)ester. After 60 min, the major reaction product exhibited a singlet at 5.8 ppm corresponding to the hydrogen *trans* to the vinyl boron. A minor compound consistent with the other alkene stereoisomer displayed a singlet at 6.2 ppm (ratio = 7:1 *E/Z*). In addition to these two

(32) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492.
(33) Chirality of Allene: (*a*) Offermann, W.; Mannschreck, A. *Org. Magn. Reson.* **1984**, *22*, 355. (*b*) Mannschreck, A.; Munninger, W.; Burgemeister, T.; Gore, J.; Cazes, B. *Tetrahedron* **1986**, *42*, 399.

stereoisomers, the non-deuterated product was also present. Unexpectedly, the alkene stereoisomer ratio diminished over time, and at ten hours a 3:1 diastereomer ratio was observed.

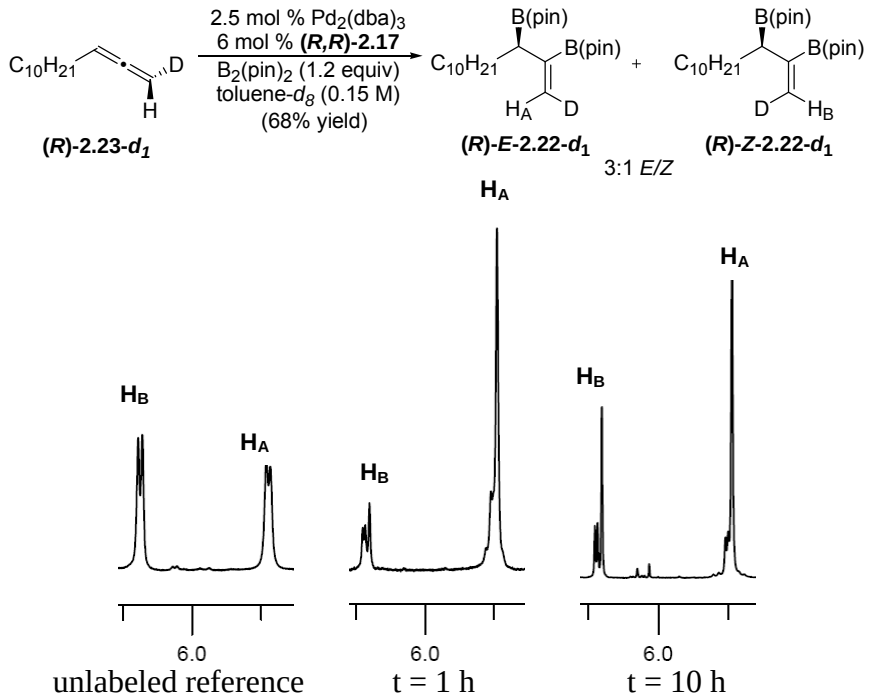
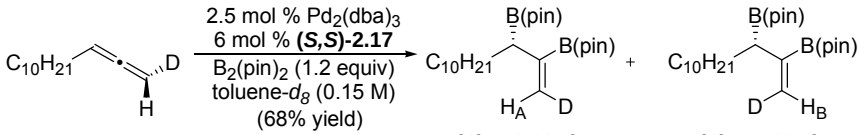


Figure 2.1. Diboration of enantiomerically enriched allene **(*R*)-2.23-*d*$_1$** with catalyst prepared from **(*R,R*)-2.17**. Reaction progress monitored by *in situ* ^{1}H NMR.

Two experiments were conducted to determine the source of the diastereochemical erosion.[18] First, the 3:1 *E/Z* mixture of **(*R*)-*E*-2.22-*d*$_1$** was resubjected to the catalytic reaction conditions and further diminution of the stereoisomer ratio was not observed. Due to the possibility that the 3:1 *E/Z* ratio might represent an equilibrium

isotope effect,[34] the diboration of **(*R*)-2.23-*d*$_1$** was conducted with **(*S,S*)-2.17** (Scheme 2.22). When ligand **(*S,S*)-2.17** was employed in the diboration a 1:3 E/Z ratio of alkene stereoisomers was obtained.

Scheme 2.22. Diboration of **(*R*)-2.23-*d*$_1$** with **(*S,S*)-2.17**

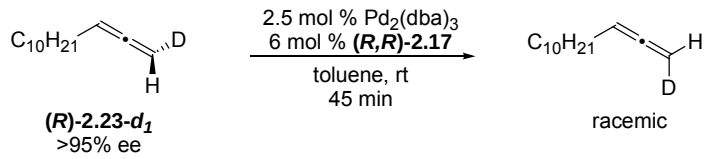


(*R*)-2.23-*d*$_1$ **(*S*)-*E*-2.22-*d*$_1$** **(*S*)-*Z*-2.22-*d*$_1$**

When the experiment described in Scheme 2.22 was repeated and halted at 90 min, racemic starting material was recovered.[18] More importantly, when **(*R*)-2.23-*d*$_1$** was treated with $Pd_2(dba)_3$ and the chiral ligand **(*R,R*)-2.17**, in the absence of $B_2(pin)_2$, the recovered starting material was found to be racemic (Scheme 2.23). This observation suggests that allene isomerization is competitive with allene diboration. The abatement of the alkene stereoisomer ratio in the diboration of **(*R*)-2.23-*d*$_1$** is due to diboration of the racemized allene. However, based on the initial selectivity from the diboration of **(*R*)-2.23-*d*$_1$** we can conclude that substrate insertion into the Pd(II)-bis(boryl) oxidative addition adduct occurs at the terminal bond of the allene.

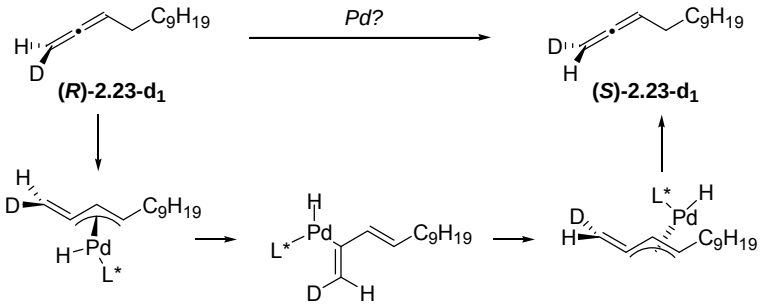
(34) (*a*) Saunders, M.; Wolfsberg, M.; Anet, F. A. L.; Kronga, O. *J. Am. Chem. Soc.* **2007**, *129*, 10276. (*b*) Ribo, J. M.; Valles, A. *J. Chem. Soc., Chem. Commun.* **1981**, 205.

Scheme 2.23. Pd-Catalyzed Racemization of **(*R*)-2.23-*d*$_1$**



2.3.4.4. Mechanism: Allene Racemization. Metal-catalyzed allene racemization has previously been observed;[35] however, mechanistic details are slight. In fact, Trost reports the synthesis of chiral allenes in the presence of $Pd_2(dba)_3$ through the dynamic kinetic asymmetric allylic alkylation of racemic allenes,[36] making the racemization of chiral allene **(*R*)-2.23-*d*$_1$** surprising. Catalytic palladium(II) will also racemize an allene in the presence of lithium bromide.[35a] This requires addition of bromide to the central carbon of the allene. It is possible that a similar mechanism operates for the racemization of **(*R*)-2.23-*d*$_1$**. Alternatively, palladium-catalyzed C-H abstraction of the allylic hydrogen, followed by formation of a vinyl palladium, rotation, and reductive elimination could also account for allene racemization (Scheme 2.24).

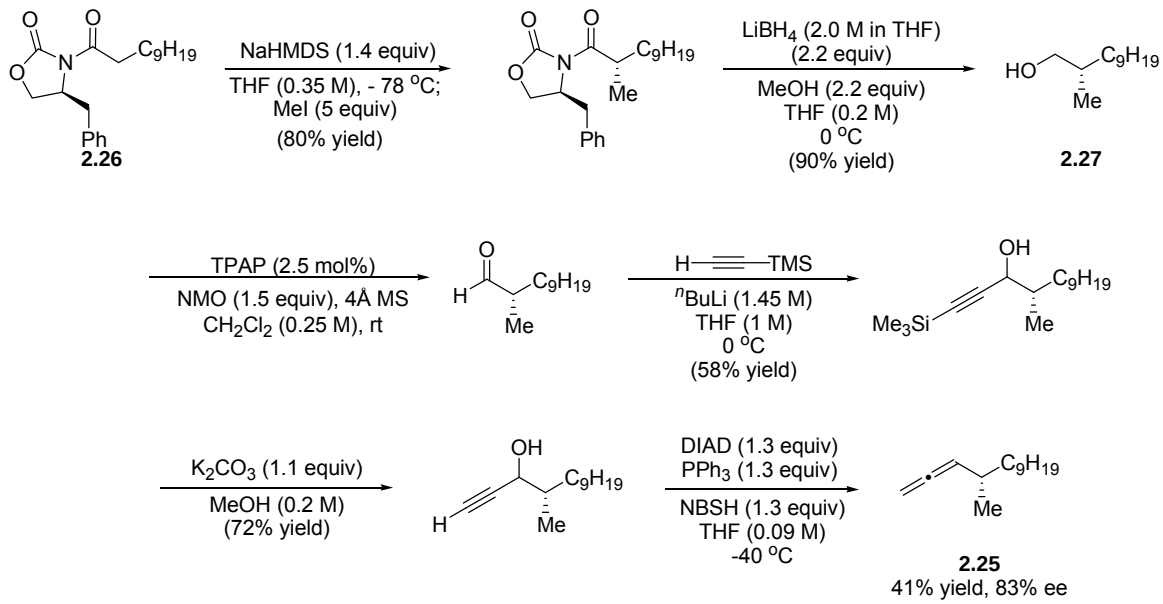
Scheme 2.24. A Potential Mechanism for the Pd-Catalyzed Allene Racemization



(35) (*a*) Horváth, A.; Bäckvall, J. *Chem. Commun.* **2004**, 964. (*b*) Claesson, A.; Olsson, L. -I. *J. Chem. Soc., Chem. Commun.* **1979**, 524.
(36) Trost, B. M.; Fandrick, D. R.; Dinh, D. C. *J. Am. Chem. Soc.* **2005**, *127*, 14186.

To determine if allene isomerization occurs by allylic CH abstraction, allene **2.25** was synthesized (Scheme 2.25). According to the mechanism is Scheme 2.24, the allylic stereocenter should be racemized as well. Methyl iodide alkylation of oxazolidinone **2.26**, followed by lithium borohydride reduction of the chiral auxillary afforded primary alcohol **2.27** in excellent yields. Ruthenium-catalyzed oxidation of the primary alcohol afforded the α-chiral aldehyde which was immediately treated with lithiated trimethylsilyl acetylene. Deprotection of the TMS group with potassium carbonate afforded a propargyl alcohol situated for allene formation. The α-chiral methyl allene **2.25** was then formed under Mitsunobu reaction conditions developed by Myers.[31]

Scheme 2.25. Synthesis of α-Methyl Allene **2.25**

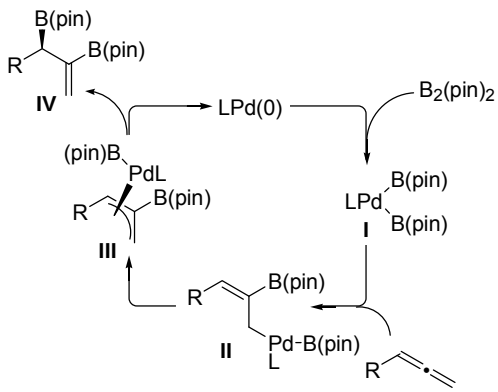


Allene **2.25** was subjected $Pd_2(dba)_3$ and ligand **(*R*,*R*)-2.17** in the absence of $B_2(pin)_2$. The allene **2.25** was recovered from the reaction mixture at time points of one

and 16 h. The enantiopurity of the recovered allene was 83% ee. Therefore, a mechanism such as that depicted in Scheme 2.24 is not operative for the Pd-catalyzed racemization of allene.

2.3.4.5. Mechanism: Kinetics. The crossover experiment and diastereodifferentiation experiment provided support for the catalytic cycle depicted in Scheme 2.26.[18] The oxidative addition $B_2(pin)_2$ to Pd to form intermediate **I** is followed by substrate insertion to yield the η^1-allyl intermediate **II**. The facial selectivity for the isomerization of η^1-allyl intermediate **II** to the π-allyl intermediate **III** is controlled by the chiral ligand on palladium. The reductive elimination of the η^3-allyl palladium intermediate affords the regioisomer of 1,2-bis(boronate)ester.

Scheme 2.26. Catalytic Cycle for Allene Diboration



Further experimental information about the catalytic cycle described above was garnered through kinetic experiments for the allene diboration reaction. It should be noted that catalyst precipitation during the course of the reaction prevented the measurement of accurate rate constants; however, the measurement of initial reaction

rates by ^{1}H NMR provided a general understanding of the catalytic cycle. In these experiments, product formation was measured against an internal standard.

The addition of excess $B_2(pin)_2$ resulted in a dramatic rate acceleration (Figure 2.2). The apparent first-order dependence on $B_2(pin)_2$ suggests that oxidative addition of the diboron to Pd may be rate-limiting, a contrast with Pt-catalyzed alkyne diboration which is first-order in [alkyne].[37] Consequentially, this observation provided a useful method for improving the reaction outcome of unreactive substrates. For example, trifluoromethyl-substituted phenyl allenes were unreactive under the standard reaction conditions but, with 3 equivalents of $B_2(pin)_2$, afford the desired product in acceptable yield (Table 2.5, entries 10-11).

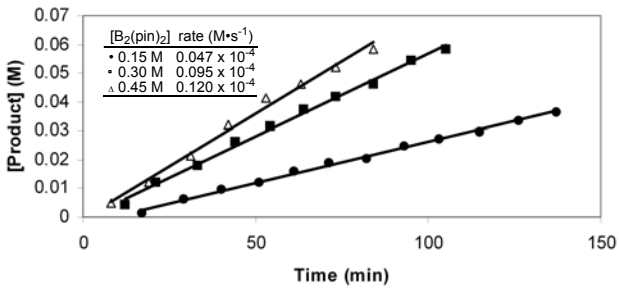


Figure 2.2. Initial reaction rates for the formation of product vs. time in the presence of 0.15 M $B_2(pin)_2$ (●), 0.30 M $B_2(pin)_2$ (■), and 0.45 M $B_2(pin)_2$ (Δ). Catalyst loading: 0.2 mol % $Pd_2(dba)_3$ and 0.48 mol % **(*R,R*)-2.17**.

The initial rates for the Pd-catalyzed diboration reaction were also measured with increasing allene concentration. The exact order of allene could not be determined due to

(37) Iverson, C. N.; Smith, M. R., III, *Organometallics* **1996**, *15*, 5155.

problems with reproducibility. However, all kinetic runs show an inverse dependence on [allene] (Figure 2.3). A possible explanation for this observation is that the allene is sequestering palladium, removing it from the catalytic cycle by forming an unreactive Pd-allene complex. Significant effort was directed toward isolation and characterization of the resting state of the active catalyst; unfortunately, these experiments did not come to fruition, but, we believe the resting state of the active catalyst is the Pd-allene complex, based on ^{31}P NMR.

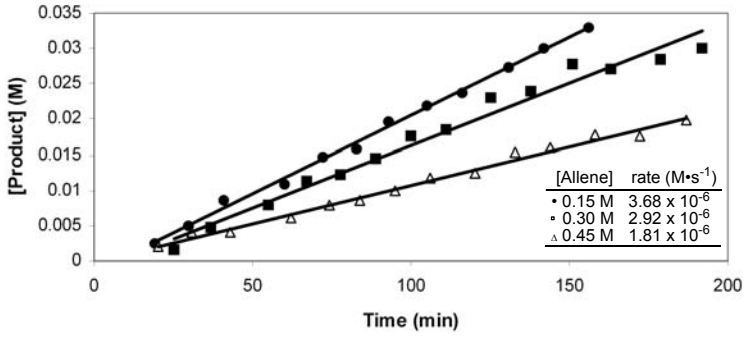


Figure 2.3. Initial reaction rates for the formation of product vs. time in the presence of 0.15 M allene (●), 0.30 M allene (■), and 0.45 M allene (Δ). Catalyst loading: 0.2 mol % $Pd_2(dba)_3$ and 0.48 mol % **(*R,R*)-2.17**.

2.3.4.6. Mechanism: Computational Studies. The above reaction mechanism is unusual in that reductive elimination releases 1,2-bis(boronate)ester **IV** from π-allyl intermediate **III** (Scheme 2.26) as opposed to releasing the regioisomeric product from intermediate **II**. To investigate this unusual reductive elimination mechanism, a series of

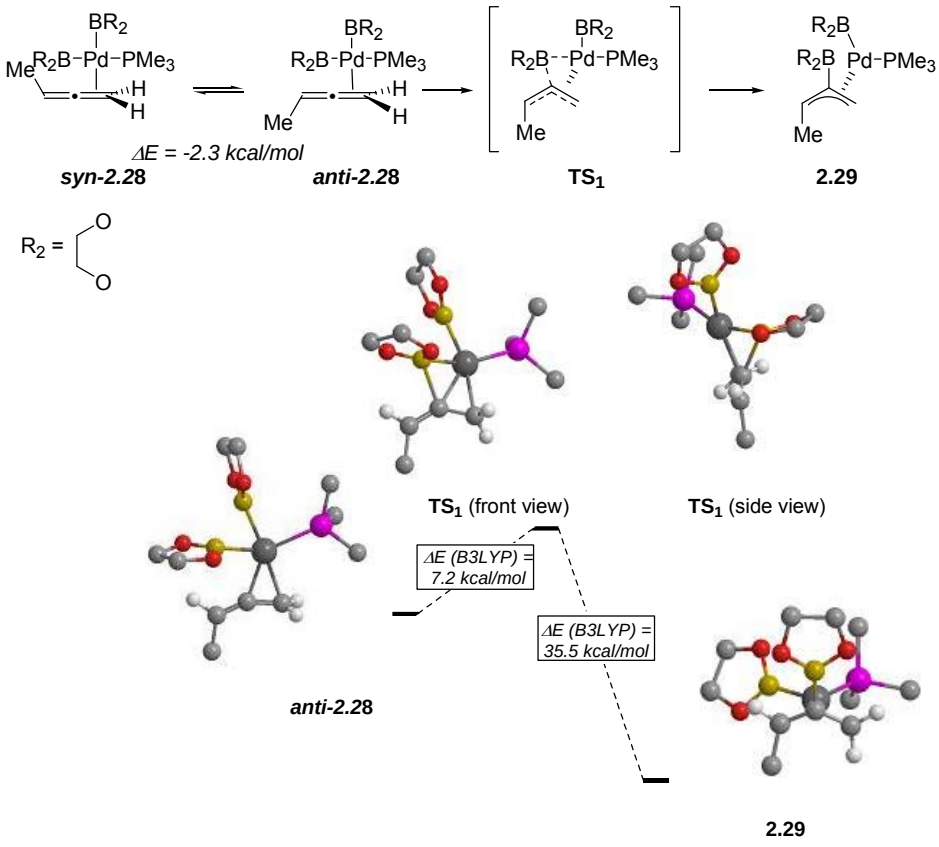
high level DFT calculations using B3LYP[38] was performed for the reaction sequence by Dr. Shubin Liu at the University of North Carolina at Chapel Hill.[18] The Stuttgart RSC 1997 ECP basis set[39] was used for Pd, and 6-311+G*[40] was used for other elements. Calculations were performed with Gaussian 03 CO2 package with tight SCF convergence and ultrafine integration grids. For transition state structure searches, a single-point frequency calculation was performed to ensure that the final structure obtained (i) has only one imaginary frequency and (ii) the vibration mode of the negative frequency corresponds to the bond formation that is anticipated. Additionally, intrinsic reaction coordinates (IRC) were calculated to verify the relevance of transition state structures. Calculations were performed with methyl allene as the substrate, PMe_3 as the ligand for palladium, and ethylene glycol as the ligand on boron.

The minimization of the η^2-allene-Pd complex **2.28** indicated that the preferred coordination of the metal to the allene is that depicted as in ***anti*-2.28** (Scheme 2.27). The η^2-allene-Pd complex ***syn*-2.28** was 2.3 kcal/mol higher in energy than the corresponding *anti* complex. Attempts to locate an energy minimum between ***anti*-2.28** and the η^1-allylic intermediate **II** (Scheme 2.26) were unsuccessful; instead, convergence on π-allyl intermediate **2.29** occurred. A single transition state (**TS_1**) was found between ***anti*-2.28** and π-allyl intermediate **2.29**; carbon-boron bond formation at the central carbon of the allene occurs concomitantly with the development of π-allyl character. A consequence of this mode of insertion is that the orientation of the ligands on palladium in π-allyl

(38) (*a*) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372. (*b*) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
(39) Bergner, A.; Dolg, M.; Kuchle, W.; Stoll, H.; Preuss, H. *Mol. Phys.* **1993**, *80*, 1431.
(40) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650.

intermediate **2.29** is dictated by their initial position in ***anti*-2.28**. Therefore, the other regioisomer of 1,2-bis(boronate)ester **IV** (Scheme 2.26) cannot be formed from the reductive elimination of **2.29** due to the spatial arrangement the ligands on palladium.

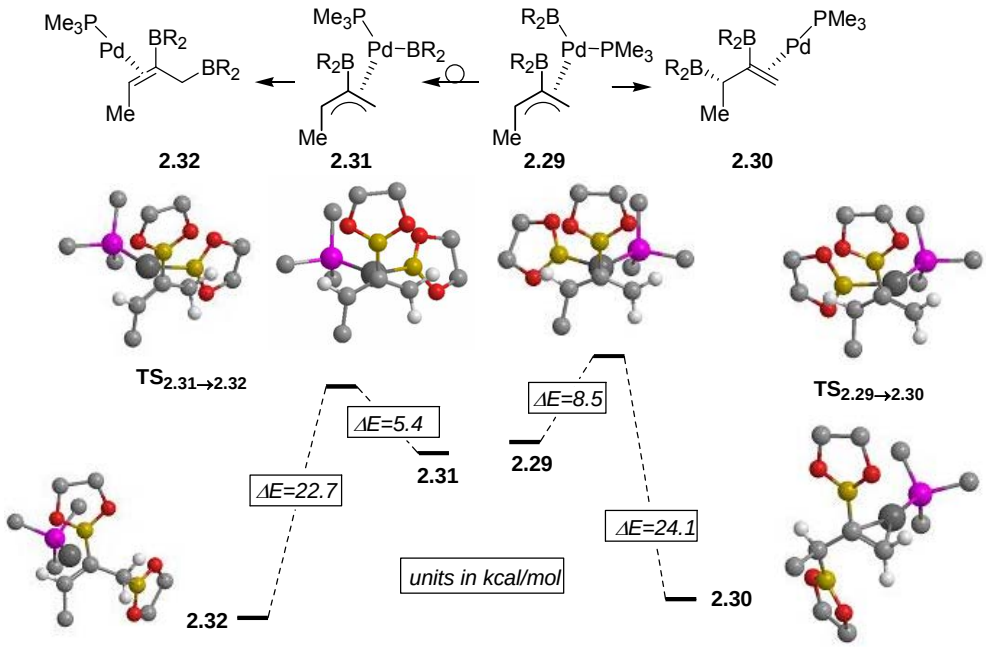
Scheme 2.27. DFT Calculations for Allene Insertion



The reductive elimination from **2.29,** in conjunction with the rotational isomer **2.31**, was investigated (Scheme 2.28). The barrier for reductive elimination from rotational isomer **2.31** is 3.1 kcal/mol lower than the barrier for reductive elimination from **2.29**. The π-allyl intermediate **2.31** is also 0.7 kcal/mol more stable than **2.29**.

Given these results, the rotational barrier between π-allyl intermediates **2.29** and **2.31** must be high, or else the other regioisomer of 1,2-bis(boronate)ester should be formed. The conversion of **2.29** to the η^1-isomer, a requirement for π-allyl isomerization, was found to be energetically uphill with the η^1 structure 9.6 kcal/mol higher in energy than the η^3 compound.

Scheme 2.28. DFT Calculations for Reductive Elimination



2.4. Conclusion

The first example of an asymmetric palladium-catalyzed diboration was reported. The diboration of prochiral monosubstituted allenes proceeds in good yields and high enantioselectivities. Through optimization of the TADDOL-derived phosphoramidite ligand scaffold, the enantiopurities for the 1,2-bis(boronate)esters obtained from the

diboration of allenes are upwards of 98% ee. Following the optimization and expansion of the substrate scope for the Pd-catalyzed allene diboration, experiments that probed the catalytic cycle were conducted. Through several experiments, we have concluded that Pd-catalyzed oxidative addition of $B_2(pin)_2$ is the rate limiting step for this transformation. Allene insertion into the Pd-bis(boryl) intermediate occurs so that the π-allyl intermediate forms at the same time that carbon-boron bond formation to the central carbon of the allene occurs. Reductive elimination from the π-allyl intermediate affords the desired 1,2-bis(boronate)ester. The other regioisomer of 1,2-bis(boronate)ester cannot be formed as a consequence of the mode of substrate insertion into the initial Pd-bis(boryl) intermediate.

2.5. Experimentals

2.5.1. General Procedure. ^{1}H NMR spectra were recorded on Bruker DRX 400 and 500 MHz as well as a Varian Unity Inova 500 MHz and Varian Gemini 400 MHz spectrometers. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and assignment. $^{13}C\{^{1}H\}$NMR spectra were recorded on a Bruker DRX 400 MHz (100 MHz), 500 (125 MHz) MHz, or Varian Unity Inova 500 MHz (125 MHz) and Varian Gemini 400 MHz (100 MHz) spectrometers. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.16 ppm). $^{31}P\{^{1}H\}$NMR (161 MHz or 202 MHz) were recorded on a Bruker DRX 400 or Varian Unity Inova 500 spectrometer. Chemical shifts are reported for ^{31}P NMR spectra using phosphoric acid as an external standard. ^{19}F NMR (376 MHz) and ^{2}H spectra (61 MHz) were recorded on a Bruker DRX 400 MHz spectrometer. Chemical shifts are reported for ^{2}H NMR spectra using $CDCl_3$ (7.26 ppm) as an internal standard. Infrared (IR) spectra were recorded on a Nicolet 560 Magna-IR and a Bruker α-P Spectrometer. Frequencies are reported in wavenumbers (cm^{-1}) as follows: strong (s), broad (br), medium (m), and weak (w). Low-resolution mass spectrometry (ESI) was performed at The University of North Carolina at Chapel Hill Mass Spectrometry Facility. High-resolution CI-GC/MS and EI were performed at Duke University, Durham, NC. MALDI-TOF was recorded at Indiana University, Bloomington, IN. High resolution ESI and DART were performed at Boston College, Chestnut Hill, MA.

Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 230 x 450 Mesh) purchased from Silicycle. Thin layer chromatography was performed on 25 μm silica gel glass backed plates from EMD Chemicals, Inc. and Silicycle. Visualization was performed using ultraviolet light, phosphomolybdic acid (PMA), and potassium permanganate ($KMnO_4$).

Analytical gas-liquid chromatography (GLC) was performed on a Hewlett-Packard 6890 Series chromatograph equipped with a CTC Analysis Combi Pal autosampler by Leap Technologies (Carrboro, North Carolina), a split mode capillary injection system, a flame ionization detector, and a Supleco β-Dex 120 column with helium as the carrier gas.

Tris(dibenzylideneacetone)dipalladium(0), mercury(II) chloride, and chlorodicarbonylrhodium(I) dimer were purchased from Strem Chemicals, Inc. Bis(pinacolato)diboron was obtained from Allychem Co., Ltd. and recrystallized from pentanes prior to use. Toluene-d_8 and acetone-d_6 were purchased from Cambridge Isotope Laboratories and were dried and degassed prior to use. 1,2-Butadiene was purchased from ChemSampCo., Inc. and used as a solution in toluene. All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Toluene and benzene were distilled over calcium hydride and degassed by freeze-pump-thaw cycles prior to use. Tetrahydrofuran was distilled from sodium and benzophenone. Triethylamine was distilled from calcium hydride. Allenes were synthesized according to literature procedures.[41] Phosphoramidite ligands were prepared

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(41) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492. (*b*) For aromatic allenes, see: Huang, C. -W.; Shanmugasundaram, M.; Chang, H. -M., Cheng, C. -H. *Tetrahedron* **2003**, *59*, 3635. (*c*) For OTBS protected allene, see: Trost, B. M.; Pinkerton, A. B.; Seidel, M. *J. Am. Chem. Soc.* **2001**, *123*, 12466.

as described in the general procedure below. TADDOL derivatives were prepared according to literature procedures.[42] All other reagents were purchased from Aldrich and used without further purification.

2.5.2. General Allene Diboration Procedures

2.5.2.1. Representative Procedure for Ligand Screening Measuring Conversion by ^1H NMR. In a dry box, a 6-dram vial with magnetic stir bar was charged with $Pd_2(dba)_3$ (3.6 mg, 3.9 μmol) and (*R,R*)-TADDOLPNMe$_2$ **(*R,R*)-2.4** (5.3 mg, 9.9 μmol) in toluene-d_8 (1.10 mL). The metal and ligand were complexed for 1 h, at which time $B_2(pin)_2$ (50.6 mg, 0.199 mmol) was added, followed by tridec-1,2-diene (30 mg, 0.166 mmol). The reaction was allowed to stir for 2 min; it was then transferred to an oven-dried NMR tube. The NMR tube was sealed with a cap and removed from the glove box. Single pulse ^{1}H NMR was used to determine the extent of reaction at 20 min.

2.5.2.2. Representative Procedure for Diboration of Allenes. A 6-dram vial with magnetic stir bar was charged with $Pd_2(dba)_3$ (7.62 mg, 0.0083 mmol), (*R,R*)-xylylTADDOLPNMe$_2$ **(*R,R*)-2.17** (13.0 mg, 0.0199 mmol), and toluene (2.2 mL) in an inert atmosphere dry box. After stirring for 1 h, $B_2(pin)_2$ (101.3 mg, 0.399 mmol) was added to the mixture followed by tridec-1,2-diene (60 mg, 0.3327 mmol). The vial was sealed with a polypropylene cap, removed from dry box, and stirred at room temperature for 12 h. The resulting solution was concentrated by rotary evaporation and purified by column chromatography on silica gel (2% ethyl acetate/hexanes), affording the 1,2-bis(boronate)ester product in 68% yield (99.7 mg).

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(42) Seebach, D.; Beck, A. K.; Keckel, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 92.

2.5.2.3. Modified Procedure for Diboration of 1,2-Butadiene. Tris(dibenzylideneacetone)dipalladium(0) (16.3 mg, 0.0178 mmol) and (*R,R*)-xylylTADDOLPNMe$_2$ **(*R,R*)-2.17** (27.7 mg, 0.0426 mmol) were complexed for 1 h in toluene (4.23 mL). The reaction was charged with $B_2(pin)_2$ (216.3 mg, 0.852 mmol) and 0.5 mL of a 1.42 M solution of 1,2-butadiene in toluene (the concentration was determined by ^{1}H NMR). The vial was sealed with a polypropylene cap, removed from the dry box, and stirred at room temperature for 14 h. The resulting solution was concentrated by rotary evaporation and purified by column chromatography (4% ethyl acetate/hexanes) on silica gel to afford 169.2 mg (77% yield) of (*R*)-4,4,5,5-tetramethyl-2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-1-en-2-yl)-1,3,2-dioxaborolane.

2.5.3. Phosphoramidite Ligand Synthesis

All phosphoramidite ligands were prepared according to the general procedure below and spectral data are in accordance with those reported in the literature. **(*R,R*)-2.4**,[43] **(*R,R*)-2.7**,[44] **(*R,R*)-2.9**,[45] **(*R,R*)-2.10**,[43] **(*R,R*)-2.11**,[46] **(*R,R*)-2.12**,[45] **(*R,R*)-2.13**,[44] **(*R,R*)-2.14**,[44] **(*R,R*)-2.15**,[43] **(*R,R*)-2.16**,[44] **(*R,R*)-2.17**.[43]

2.5.3.1. General Procedure for (R,R)-TADDOL-Phosphoramidite Ligand Synthesis. To an oven-dried flask with magnetic stir bar, under nitrogen, was added flame-dried 4Å molecular sieves, the respective TADDOL derivative (1 equiv), and tetrahydrofuran

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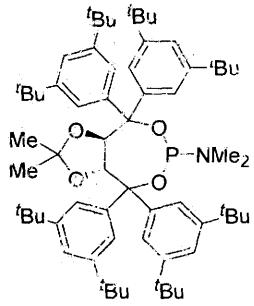
(43) Pfretzschner, T.; Kleemann, L.; Janza, B.; Harms, K.; Schrader, T. *Chem. –Eur. J.* **2004**, *10*, 6048.
(44) Boele, M. D. K.; Kamer, P. C. J.; Lutz, M.; Spek, A. L.; de Vries, J. G.; van Leeuwen, P. W. N. M.; van Strijdonck, G. *Chem. –Eur. J.* **2004**, *10*, 6232.
(45) Alexakis, A.; Burton, J.; Vastra, J.; Benhaim, C.; Fournioux, X.; Heuvel, A.; Leveque, J.-M.; Maze, F.; Rosset, S. *Eur. J. Org. Chem.* **2000**, 4011.
(46) Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 12370.

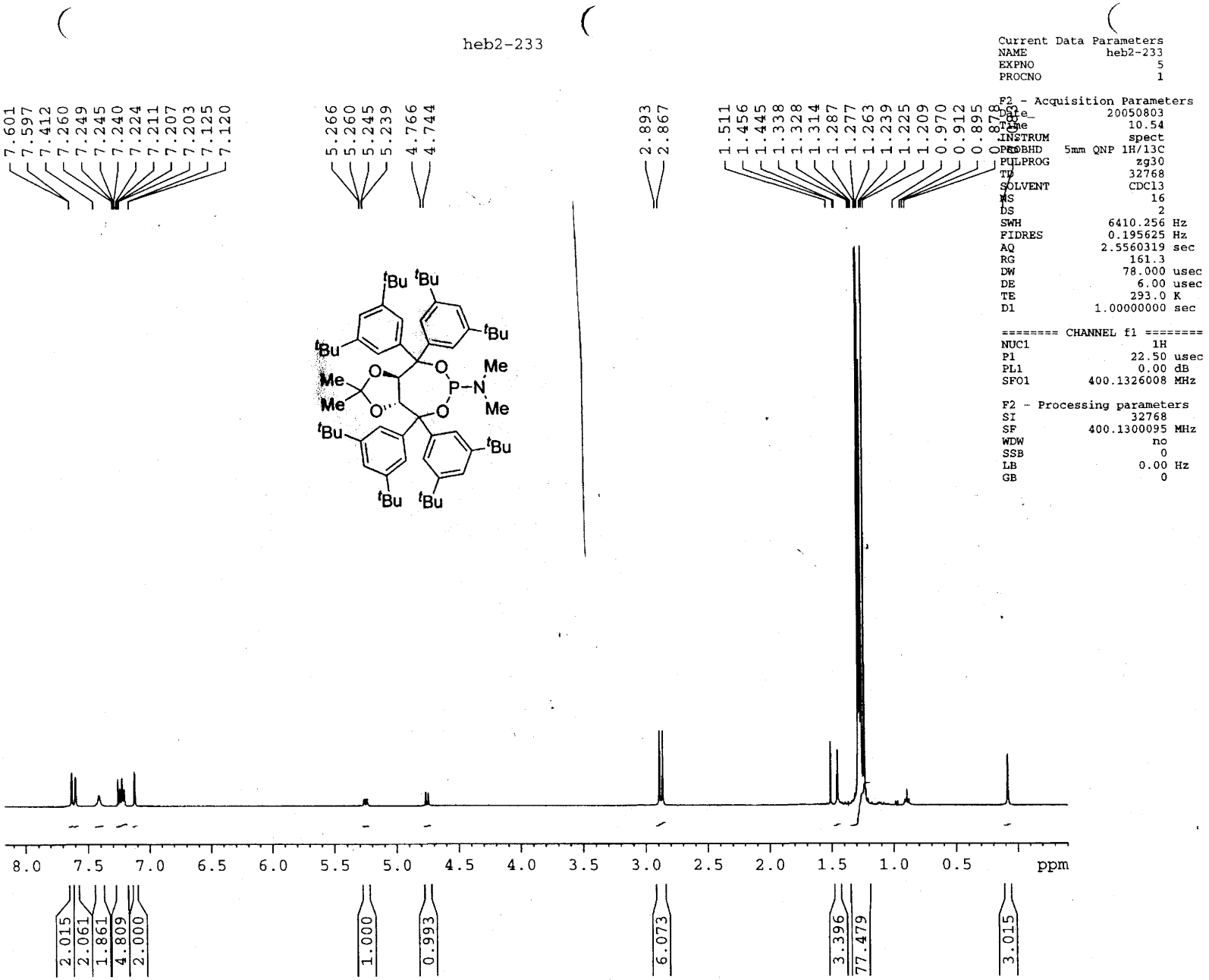
([TADDOL] = 0.25 M). The flask was cooled to 0 °C (ice-water bath) and charged with triethylamine (3.4 equiv) followed by phosphorus trichloride (1.2 equiv). The mixture was warmed to ambient temperature and stirred for 30 min. The reaction mixture was then cooled to 0 °C (ice-water bath) and charged with dimethylamine in tetrahydrofuran (10 equiv) or the other amine (5 equiv, neat). The reaction was allowed to stir overnight at ambient temperature, at which time it was diluted with diethyl ether, and filtered over Celite. The solvent was removed by rotary evaporation and the unpurified mixture was purified by column chromatography on silica gel.

2.5.3.2. Preparation of 3,5-(^{t}Bu)$_2$TADDOLPNMe$_2$ (R,R)-2.18. To a 250-mL flame-dried round bottom flask equipped with an oven-dried magnetic stir bar was added flame-dried 4Å molecular sieves, followed by 3,5-(^{t}Bu)$_2$TADDOL (5.573 g, 6.087 mmol, 1 equiv) and tetrahydrofuran (25 mL, 0.25 M). The flask was cooled to 0 °C (ice-water bath) and charged with triethylamine (2.88 mL, 20.69 mmol, 3.4 equiv) and phosphorus trichloride (637 μL, 7.305 mmol, 1.2 equiv). The mixture was allowed to warm to ambient temperature and stirred for 30 min, at which time it was cooled to 0 °C (ice-water bath) and charged with dimethylamine (30 mL, 2.0 M in tetrahydrofuran, 10 equiv). The mixture was warmed to ambient temperature, stirred overnight, and was diluted with diethyl ether, and filtered over Celite. Solvent was removed by rotary evaporation and the unpurified reaction mixture was purified by column chromatography on silica gel (4% ethyl acetate/hexanes) to afford the desired phosphoramidite (3.95 g, 65% yield).



(*R,R*)-2.18

(3a*R*,8a*R*)-4,4,8,8-Tetrakis(3,5-di-*tert*-butylphenyl)-*N*,*N*-dimethyl-tetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-amine (*R,R*)-2.18. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (3H, s, CH_3CO), 1.24 (18H, s, $(CH_3)_3CAr$), 1.26 (18H, s, $(CH_3)_3CAr$), 1.28 (18H, s, $(CH_3)_3CAr$), 1.29 (18H, s, $(CH_3)_3CAr$), 1.46 (3H, s, CH_3CO), 2.88 (6H, d, J = 10.4 Hz, $(CH_3)_2N$), 4.76 (1H, d, J = 8.8 Hz, OC**H**C), 5.25 (1H, dd, J = 8.4, 2.4 Hz, OC**H**C), 7.12 (2H, d, J = 2 Hz, Ar**H**), 7.20-7.25 (4H, m, Ar**H**), 7.41 (2H, s, Ar**H**), 7.60 (2H, d, J = 1.6 Hz, Ar**H**), 7.63 (2H, d, J = 1.6 Hz, Ar**H**). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 28.2, 31.65, 31.69, 31.7, 34.9, 35.0, 35.1, 35.5, 35.7, 81.4, 81.5, 82.4, 82.5, 83.9, 83.9, 84.1, 110.0, 120.1, 120.4, 120.7, 121.6, 123.8, 123.9, 123.9, 141.2, 142.0, 146.20, 146.23, 146.6, 148.8, 149.0, 149.3, 149.7. ^{31}P NMR (161 MHz, $CDCl_3$) δ 141.9. IR(CH_2Cl_2): 3437 (w, br), 3064 (s), 2959 (s), 2900 (s), 2854 (s), 2792 (s), 2753 (s), 2709 (s), 2353 (s), 2326 (s), 2287 (s), 1778 (s), 1592 (s), 1475 (s), 1392 (s), 1366 (s), 1254 (s), 1190 (s), 1053 (s), 968 (s), 894 (s), 870 (s), 785 (s), 734 (s), 696 (s) cm^{-1}. HRMS-(ESI+): for $C_{65}H_{98}NO_4P$ calc'd: 988.7312 $(M+H)^+$, observed: 988.7306 $(M+H)^+$. Purification: silica gel with 4% ethyl acetate/hexanes afforded the desired phosphoramidite (3.95 g, 65% yield) as a white solid. R_f = 0.52 (2% ethyl acetate/hexanes, stain in PMA).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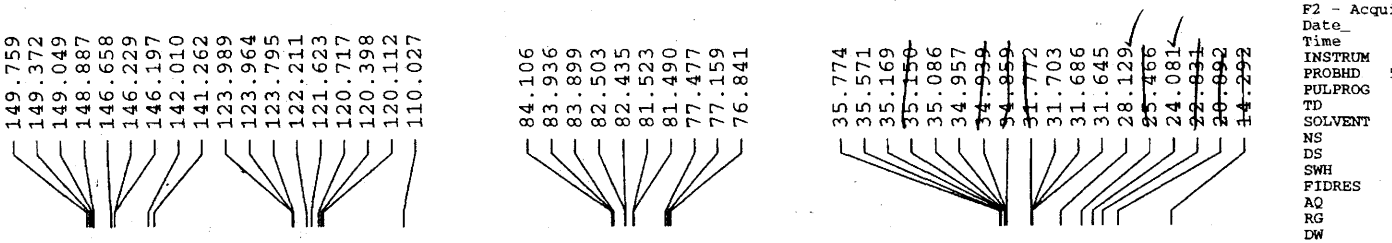

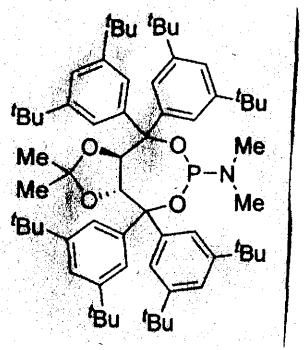

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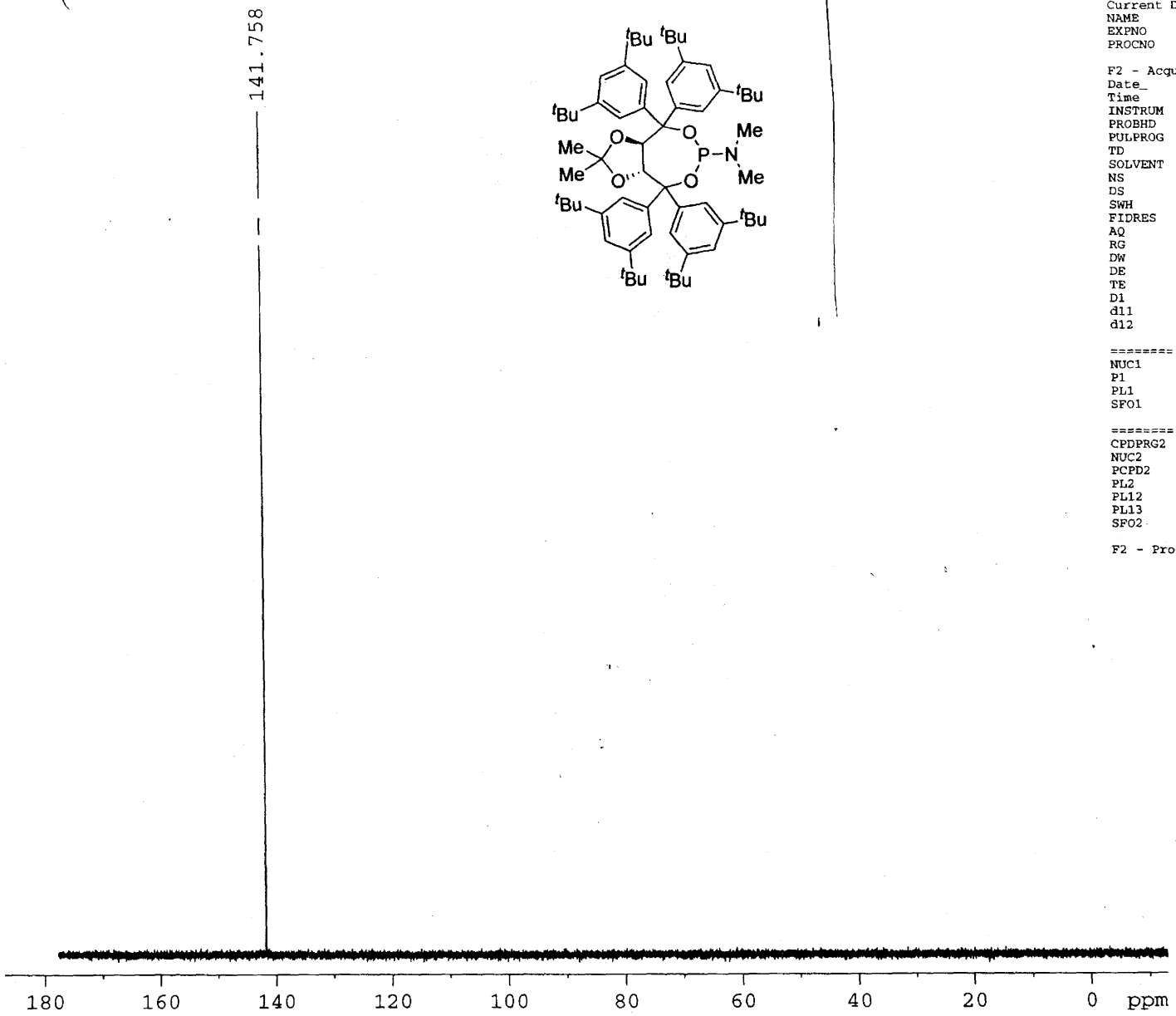

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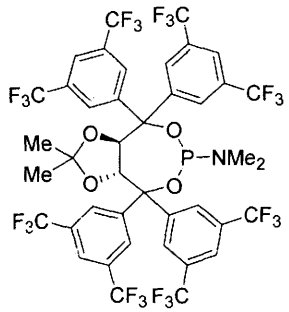
F2 - Processing parameters

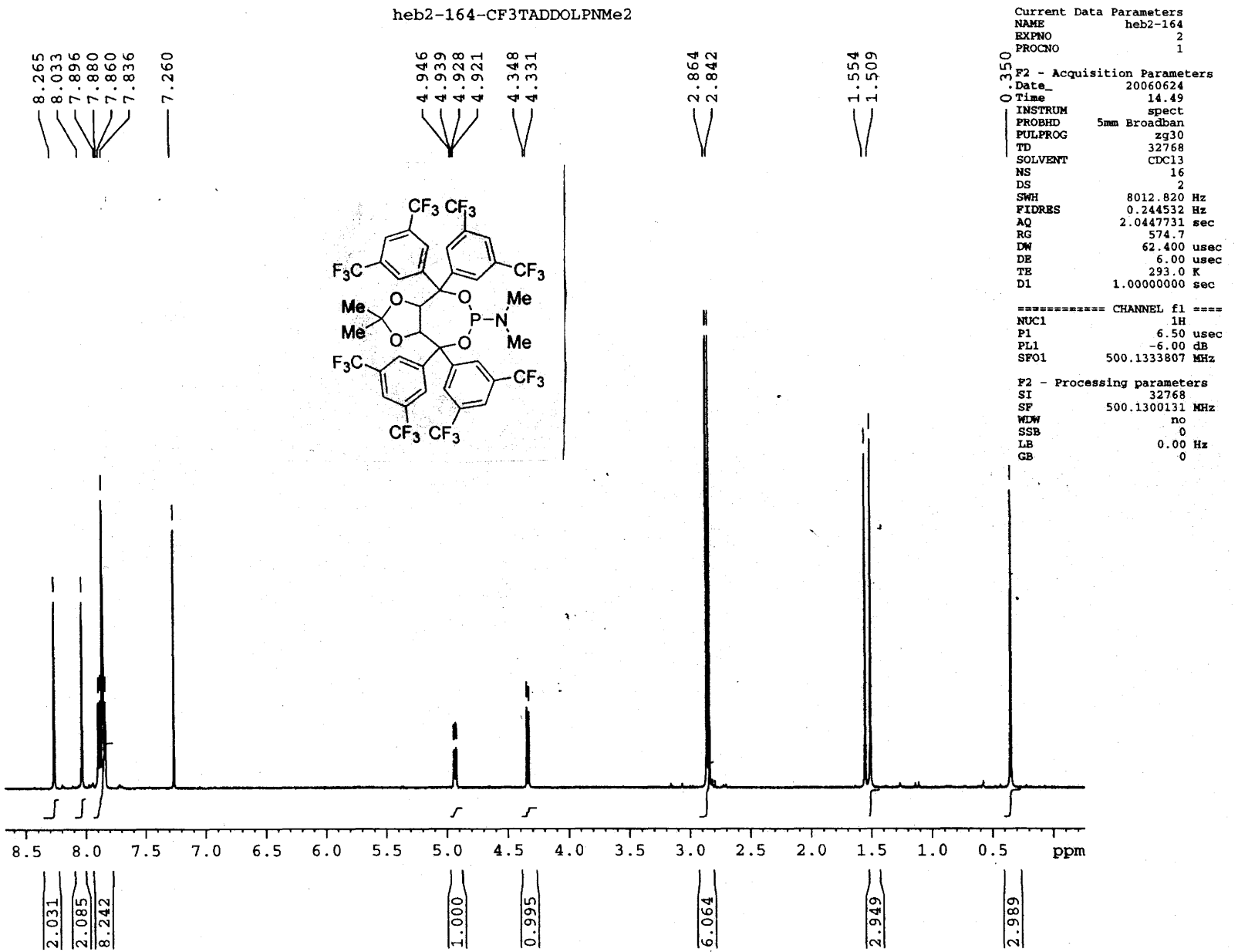
2.5.3.3. Preparation of 3,5-$(CF_3)_2$TADDOLPNMe$_2$ (R,R)-2.19. To a 100-mL round-bottom flask equipped with an oven-dried magnetic stir bar, was added 4Å molecular sieves, followed by 3,5-$(CF_3)_2$TADDOL (2.43 g, 2.40 mmol, 1 equiv) and tetrahydrofuran (9.6 mL, 0.25 M). The flask was cooled to 0 °C (ice-water bath) and charged with triethylamine (1.13 mL, 8.16 mmol) followed by phosphorus trichloride (251 μL, 2.88 mmol). The mixture was allowed to warm to ambient temperature and stirred for 30 min, at which time it was cooled to 0 °C (ice-water bath) and charged with dimethylamine (12 mL, 2.0 M in tetrahydrofuran). The mixture was warmed to ambient temperature and allowed to stir overnight. At which time, the reaction mixture was diluted with diethyl ether and filtered over Celite. The solvent was removed by rotary evaporation and the unpurified reaction mixture was purified by column chromatography on silica gel (10% dichloromethane/hexanes), and then recrystallized from dichloromethane to afford phosphoramidite **(*R,R*)-2.19** (597 mg, 22% yield) as a white solid.



(*R,R*)-2.19

(3a*R*,8a*R*)-4,4,8,8-Tetrakis(3,5-bis(trifluoromethyl)phenyl)-*N,N*-dimethyl-tetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-amine (*R,R*)-2.19. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.35 (3H, s, C**H$_3$**CCH$_3$), 1.51 (3H, s, CH$_3$CC**H$_3$**), 2.85 (6H, d, J = 11.0 Hz, (C**H$_3$**)$_2$N), 4.33 (1H, d, J = 8.5 Hz, OC**H**C), 4.94 (1H, dd, J = 9.0, 3.5 Hz, OC**H**C), 7.83-7.89 (8H, m, Ar**H**), 8.03 (2H, s, Ar**H**), 8.30 (2H, s, Ar**H**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.4, 27.2, 35.2 (2C, d, $^2J_{CP}$ =

20.2 Hz), 79.7, 80.2 (1C, d, $^{2}J_{CP}$ = 8.2 Hz), 81.9 (1C, d, $^{3}J_{CP}$ = 22.2 Hz), 82.9 (1C, d, $^{3}J_{CP}$ = 3.1 Hz), 113.4, 122.5 (1C, q, $^{3}J_{CF}$ = 3.5 Hz), 122.6 (1C, q, $^{3}J_{CF}$ = 3.6 Hz), 122.9 (1C, q, $^{3}J_{CF}$ = 3.7 Hz, 123.0 (1C, q, $^{3}J_{CF}$ = 3.5 Hz), 123.24 (4C, q, $^{1}J_{CF}$ = 272.6 Hz), 123.25 (2C, q, $^{1}J_{CF}$ = 272.7 Hz), 123.3 (2C, q, $^{1}J_{CF}$ = 272.2 Hz), 126.8 (2C), 127.0 (2C), 128.7 (2C), 128.8 (2C), 131.6 (2C, q, $^{2}J_{CF}$ = 33.5 Hz), 132.12 (2C, q, $^{2}J_{CF}$ = 33.5 Hz), 132.15 (2C, q, $^{2}J_{CF}$ = 33.2 Hz), 132.6 (2C, q, $^{2}J_{CF}$ = 34.2 Hz), 141.8, 142.7, 146.5, 147.4. ^{31}P NMR (202 MHz, $CDCl_3$) δ 140.7. ^{19}F (376 MHz, $CDCl_3$) δ -63.8 (6F, s), -63.7 (6F, s), -63.6 (6F, s), -63.5 (6F, s). LRMS–(ESI+): for $C_{41}H_{27}F_{24}NO_4P$ calc'd: 1084.12 $(M+H)^+$, observed: 1084.2 $(M+H)^+$. Purification: The ligand is very sensitive to silica gel and will decompose on the column. The ligand was eluated with 10% dichloromethane/hexanes and further purified by recrystallization from dichloromethane to afford 597 mg (22% yield) of a white solid. R_f = 0.51 (10% dichloromethane/hexanes, stain in PMA).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4.921
4.348
4.331
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DE 6.00 usec
TE 293.0 K
D1 1.00000000 sec
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F2 - Processing parameters
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SF 500.1300131 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
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CF3
Me
Me
O
O
P-N
Me
Me
O
O
F3C
CF3
CF3 CF3
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
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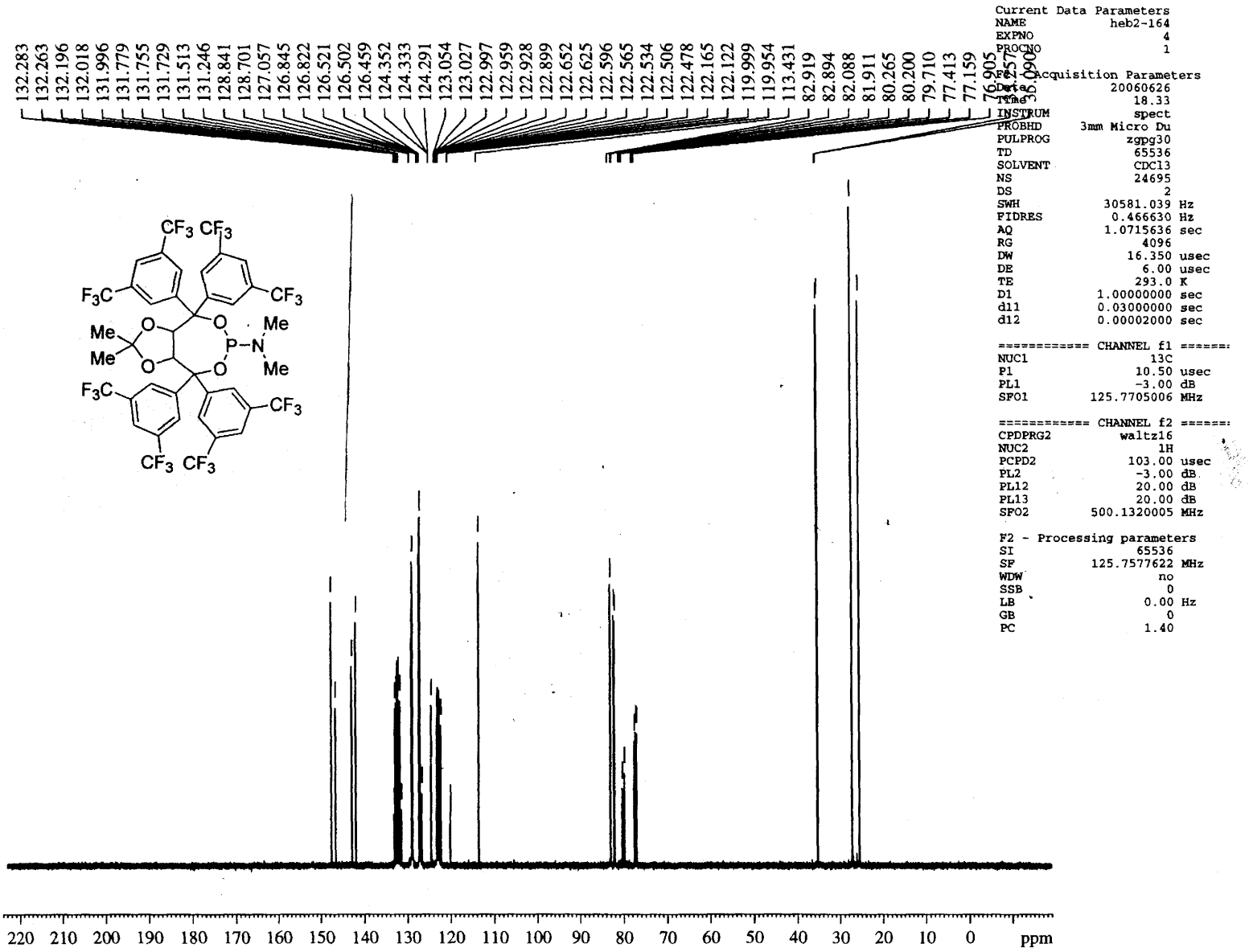
2.949
2.989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81.911
80.265
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77.159
76.905
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77.090
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PROCNO 1
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SWH 30581.039 Hz
FIDRES 0.466630 Hz
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RG 4096
DW 16.350 usec
DE 6.00 usec
TE 293.0 K
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d11 0.03000000 sec
d12 0.00002000 sec
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PL1 -3.00 dB
SFO1 125.7705006 MHz
CHANNEL f2
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PCPD2 103.00 usec
PL2 -3.00 dB
PL12 20.00 dB
PL13 20.00 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
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SF 125.7577622 MHz
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SSB 0
LB 0.00 Hz
GB 0
PC 1.40
CF3 CF3
F3C
CF3
Me
O
O
P–N
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O
O
Me
F3C
CF3
CF3 CF3
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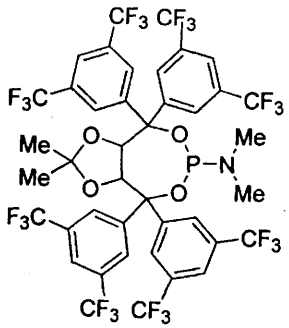

TADDOLPNMe2

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77

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TD                      65536
SOLVENT                 CDCl3
NS                         64
DS                          2
SWH                 64102.562 Hz
FIDRES              0.978127 Hz
AQ                  0.5112308 sec
RG                    18390.4
DW                      7.800 use
DE                      6.00 use
TE                     293.0 K
D1                 2.00000000 sec
d11                0.03000000 sec
d12                0.00002000 sec

============ CHANNEL f1 ===
NUC1                      31P
P1                      12.70 use
PL1                      0.00 dB
SFO1             202.4561427 MHz

============ CHANNEL f2 ===
CPDPRG2                waltz16
NUC2                       1H
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PL2                     -3.00 dB
PL12                    14.00 dB
PL13                    14.00 dB
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F2 - Processing parameters
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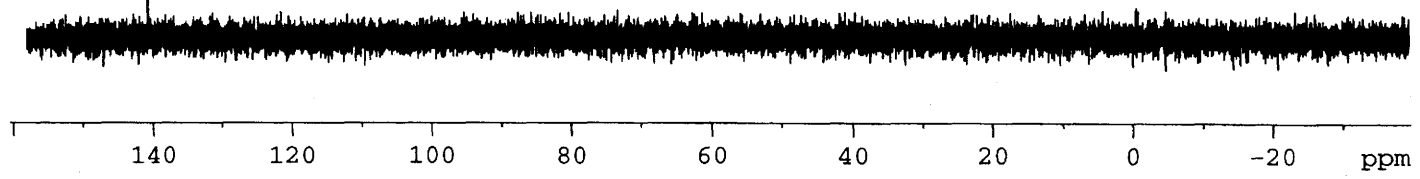
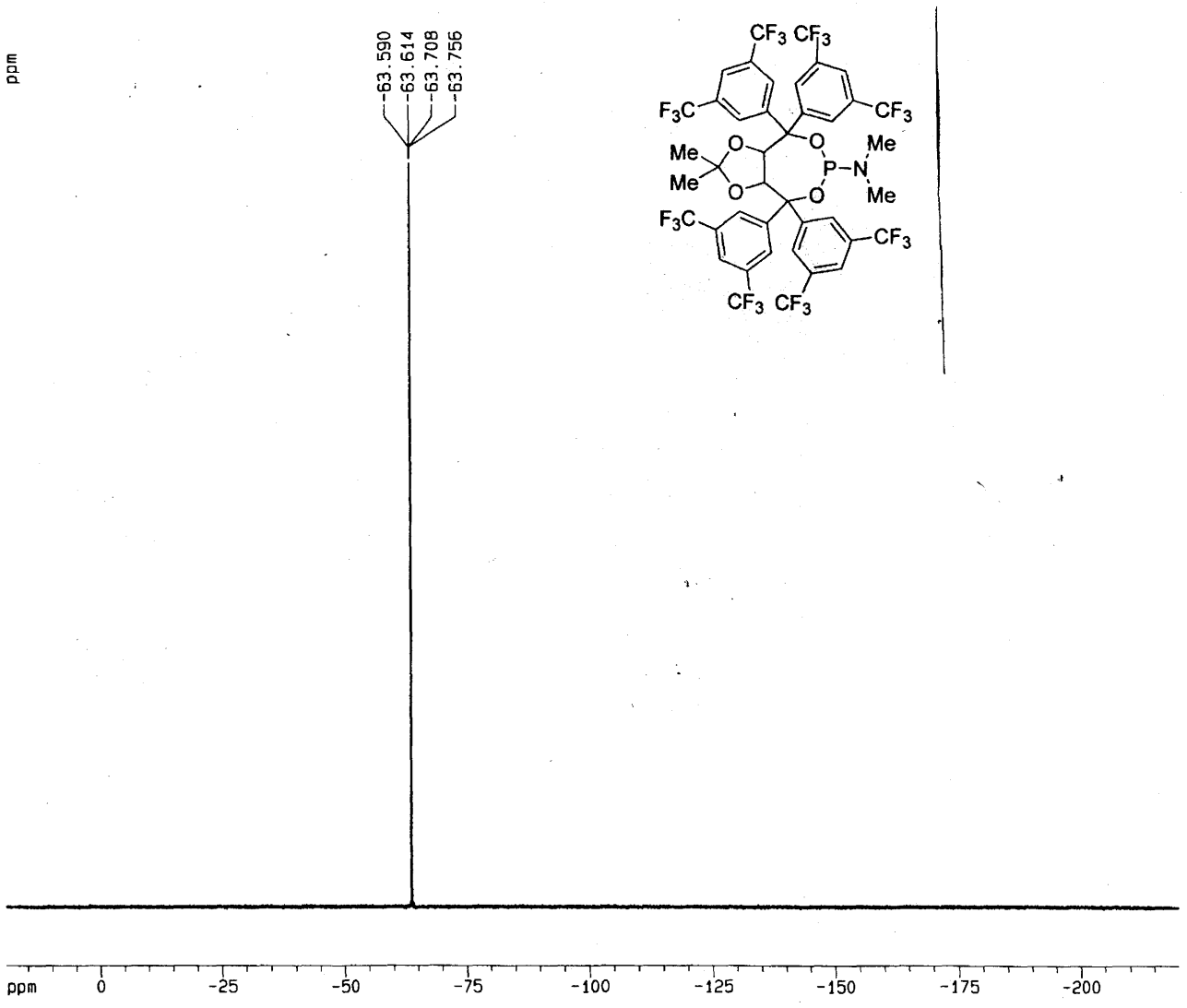


heb3-264-19F



Current Data Parameters

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EXPNO	22
PROCNO	1

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PULPROG	zgflqn
TD	131072
SOLVENT	CDCl3
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DS	4
SWH	90090.094 Hz
FIDRES	0.687333 Hz
AQ	0.7275051 sec
RG	2896.3
DW	5.550 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

======== CHANNEL f1 ========

NUC1	19F
P1	18.00 usec
PL1	0.00 dB
SFO1	376.3856167 MHz

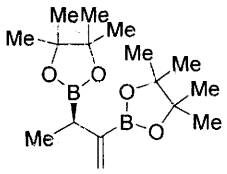
F2 - Processing parameters

SI	65536
SF	376.4233185 MHz
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
CY	12.50 cm
F1P	19.508 ppm
F1	7343.21 Hz
F2P	-219.824 ppm
F2	-82746.88 Hz
PPMCM	11.96659 ppm/cm
HZCM	4504.50439 Hz/cm

2.5.4. Characterization of Substrates in Table 2.5

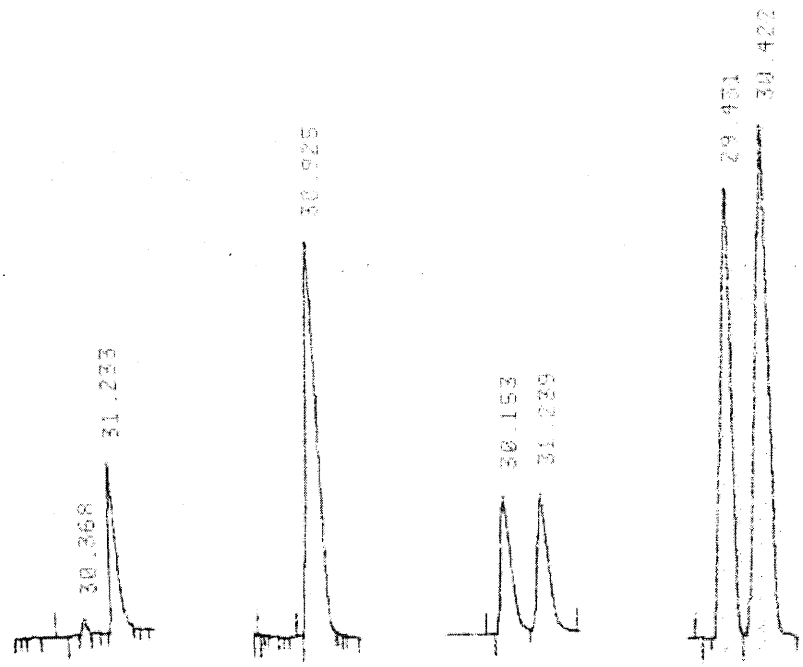


(*R*)-4,4,5,5-Tetramethyl-2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-1-en-2-yl)-1,3,2-dioxaborolane (Table 2.5, entry 2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (3H, d, J = 7.2 Hz, CH_3CHB), 1.23 (12H, s, OCCH_3), 1.26 (12H, s, OCCH_3), 2.03 (1H, q, J = 7.2 Hz, CH_3C**H**B), 5.55 (1H, br s, C**H**CB), 5.74 (1H, d, J = 4 Hz, C**H**CB). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 24.8 (4C), 24.9 (4C), 83.2, 83.4, 125.9. IR (neat): 2978 (s), 2933 (s), 2874 (s), 1612 (s), 1464 (m, br), 1423 (m, br), 1378 (m, br) cm^{-1}. HRMS-(ESI+): for $C_{16}H_{30}B_2O_4$ calc'd: 331.2228 $(M+Na)^+$, observed: 331.2229 $(M+Na)^+$. Purification: silica gel with 4% ethyl acetate/hexanes as the eluant provided 74 mg of a yellow oil (72% yield). R_f = 0.32 (4% ethyl acetate/hexanes, stain in PMA).

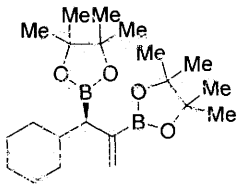
Proof of Stereochemistry. Configuration and stereoisomer ratios were determined by diimide reduction (2-nitrobenzenesulfonylhydrazide,[47] triethylamine, dioxanes, 95 °C) of the vinyl boronate followed by basic hydrogen peroxide oxidation (3 M NaOH, H_2O_2, quench with $Na_2S_2O_3$). The resulting diol was compared to commercially available racemic 2,3-butanediol and (2*R*,3*R*)-(-)-butanediol, purchased from Aldrich.

(47) Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507.

Chiral GLC (β-dex, Supelco, 50 °C, 1 deg/min) – analysis of 2,3-butanediol – from reduction and oxidation of reaction product.



Diboration Product | Authentic | Racemic | Diboration Product & Racemic



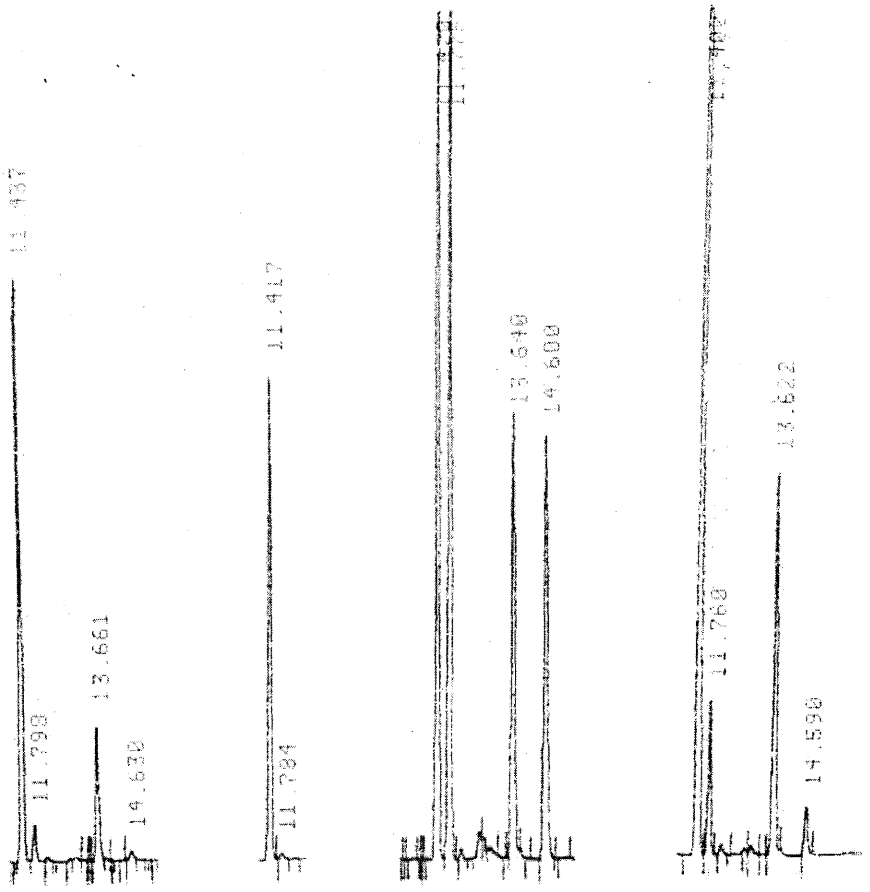
(*R*)-2-(1-Cyclohexyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 2.5, entry 3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80-1.4 (5H, m, Cy**H**), 1.19 (6H, s, OCC**H**$_3$), 1.20 (6H, s, OCC**H**$_3$), 1.24 (12H, s, OCC**H**$_3$), 1.60-1.80 (7H, m, Cy**H** and CHC**H**B), 5.63 (1H, d, J = 2.8 Hz, CBC**H**), 5.82 (1H, d, J = 3.2 Hz, CBC**H**). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 26.6 (2 C), 26.7 (1C), 26.9 (2C), 32.8, 33.7, 38.5, 82.9, 83.3, 129.3. IR (neat): 3062 (s), 2978 (s), 2923 (br), 2850 (s), 1604 (s), 1371 (br, m) cm^{-1}. HRMS-(ESI): for $C_{21}H_{38}B_2O_4$ calc'd: 399.2854 $(M+Na)^+$, observed: 399.2871 $(M+Na)^+$. Purification: silica gel with 4% ethyl acetate/hexanes afforded 97 mg (60% yield) of a yellow oil. R_f = 0.32 (4% ethyl acetate/hexanes, stain in PMA).

Proof of Stereochemistry. Configuration and stereoisomer ratios were determined by diimide reduction (2-nitrobenzenesulfonylhydrazide,[47] triethylamine, dioxanes, 95 °C) of the vinyl boronate followed by basic hydrogen peroxide oxidation (3 M NaOH, H_2O_2, quench with $Na_2S_2O_3$). The resulting diol was protected as the acetonide (*p*-toluenesulfonic acid and 2,2-dimethoxypropane). Racemic material was prepared from the diboration of propa-1,2-dienyl-cyclohexane as described in the general procedure using tricyclohexylphosphine. The diboron was then reduced, oxidized, and protected as described above. Configuration was established by hydrogenation of (1*R*, 2*R*)-1-phenyl-propane-1,2-diol (prepared via Sharpless asymmetric dihydroxylation)[48] with rhodium on

(48) Norrby, P. -O.; Becker, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1996**, *118*, 35.

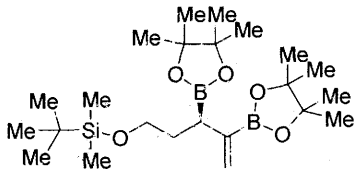
alumina, glacial acetic acid, and H_2 (60 psi).[49] The resulting diol was protected as the acetonide (*p*-toluenesulfonic acid and 2,2-dimethoxypropane).

Chiral GLC (β-dex, Supelco, 120 °C) -- analysis of acetonide derived from reduction and oxidation of reaction product as described above.



Diboration Product | Authentic | Racemic | Diboration Product & Racemic

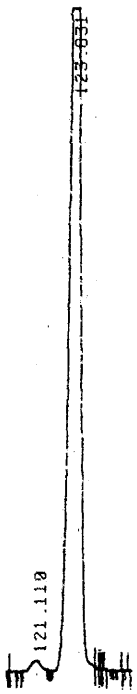
(49) Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515.



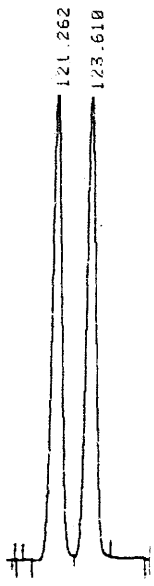
(*R*)-(3,4-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-4-enyloxy)(*tert*-butyl)dimethylsilane (Table 2.5, entry 6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.003 (6H, s, $(CH_3)_2Si$), 0.89 (9H, s, $(CH_3)_3CSi$), 1.19 (6H, s, $OCCH_3$), 1.20 (6H, s, $OCCH_3$), 1.22 (12H, s, $OCCH_3$), 1.74 (1H, m, $CH_2CH_AH_BCHB$), 1.85 (1H, m, $CH_2CH_AH_BCHB$), 1.98 (1H, t, J = 7.4 Hz, CH_2CHBCB), 3.55 (2H, m, OCH_2CH_2), 5.55 (1H, d, J = 2.4 Hz, CHCB), 5.75 (1H, d, J = 3.2 Hz, CHCB). ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.1, -5.07, 18.5, 24.7 (2C), 24.8 (2C), 24.9 (2C), 25.0 (2C), 26.2 (3C), 32.7, 63.0, 83.1 (2C), 83.4 (2C), 128.0. IR (neat): 3055 (w), 2973 (s), 2848 (s), 2734 (w), 2289 (w), 1610 (s), 1475 (s), 1361 (s), 1274 (s), 1241 (s) cm^{-1}. LRMS-(ESI+): for $C_{23}H_{46}B_2NaO_5Si$ calc'd: 475.3 $(M+Na)^+$, observed: 475.3 $(M+Na)^+$. Purification: silica gel with 5% ethyl acetate/hexanes afforded 162 mg (68% yield) of a yellow oil. R_f = 0.33 (5% ethyl acetate/hexanes, stain in PMA).

Proof of Stereochemistry. Configuration and stereoisomer ratios were determined by diimide reduction (2-nitrobenzenesulfonylhydrazide (3 equiv),[47] triethylamine (6 equiv), dioxanes (0.1 M), 80 °C, overnight) of the vinyl boronate followed by basic hydrogen peroxide oxidation (3 M NaOH, H_2O_2, quench with $Na_2S_2O_3$). The resulting diol was protected as the diacetate (acetic anhydride (1.2 equiv), triethylamine (3 equiv), and 4-dimethylaminopyridine (cat.) in dichloromethane (0.25 M)). Racemic material was prepared from the diboration of *tert*-butyldimethyl(penta-3,4-dienyloxy)silane as described in the general procedure using tricyclohexylphosphine.

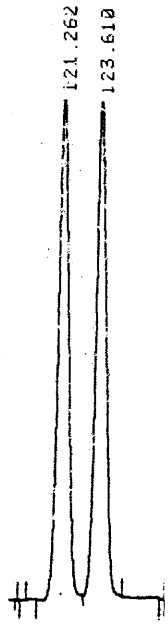
Chiral GLC (β-dex, Supelco, 100 °C for 25 min then 0.5 deg/min to 120 °C) – analysis of acetate derived from reduction and oxidation of reaction product as described above



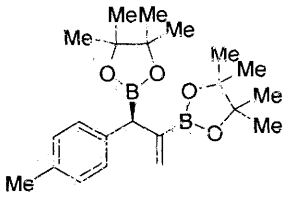
Diboration Product



Racemic



Diboration Product & Racemic

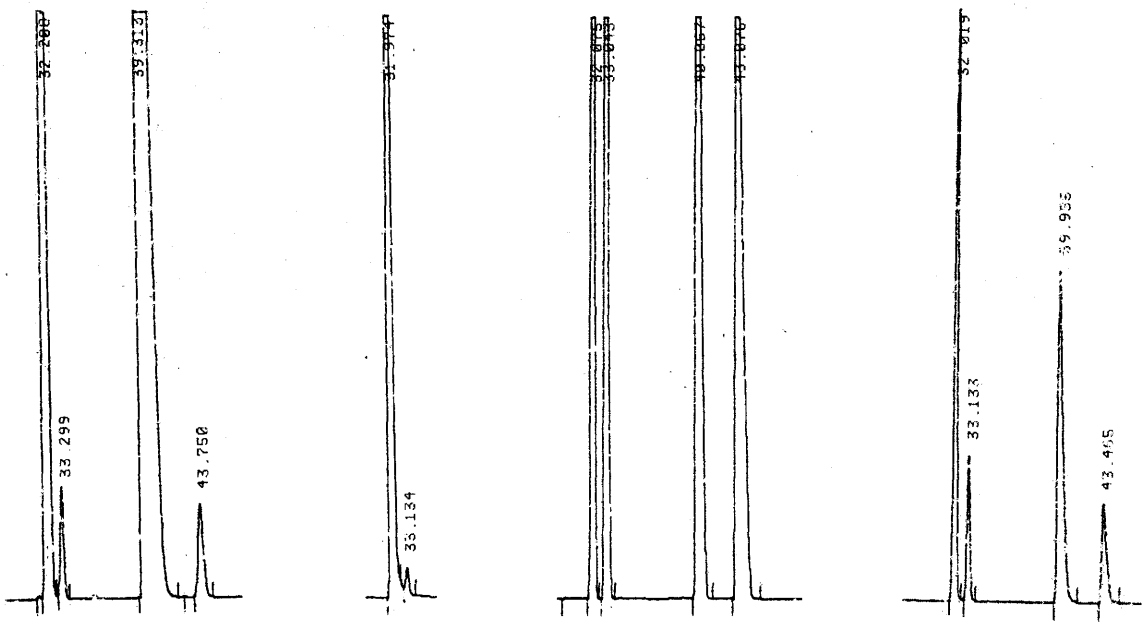


(*S*)-4,4,5,5-Tetramethyl-2-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-*p*-tolylprop-2-en-2-yl)-1,3,2-dioxaborolane (Table 2.5, entry 8). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (6H, s, OCC**H**$_3$), 1.27 (12H, s, OCC**H**$_3$), 1.28 (6H, s, OCC**H**$_3$), 2.31 (3H, s, C**H**$_3$Ar), 3.35 (1H, s, ArC**H**B), 5.28 (1H, t br, J = 2.4 Hz, CBC**H**), 5.83 (1H, q br, J = 2.8, 1.6 Hz, CBC**H**), 7.09 (4H, s, Ar**H**). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 24.6 (2C), 24.7 (2C), 24.9 (2C), 25.0 (2C), 83.5 (2C), 83.6 (2C), 127.9, 129.0 (2C), 129.9 (2C), 134.8, 134.7. IR (neat): 2976 (s), 2926 (s), 2867 (w), 2731 (w), 2291 (w), 2244 (w), 1890 (w), 1610 (s), 1513 (s), 1412 (br) cm^{-1}. LRMS-(ESI+): for $C_{22}H_{35}B_2O_4$ calc'd: 385.2 $(M+H)^+$, observed: 385.2 $(M+H)^+$. Purification: silica gel with 2% ethyl acetate/hexanes afforded 216.9 mg (71% yield) of a yellow oil. R_f = 0.24 (4% ethyl acetate/hexanes, stain in PMA).

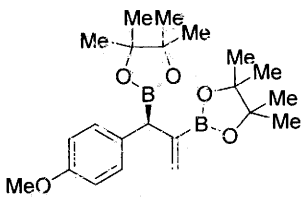
Proof of Stereochemistry. Configuration and stereoisomer ratios were determined by diimide reduction (2-nitrobenzenesulfonylhydrazide (3 equiv),[47] triethylamine (6 equiv), dioxanes (0.1 M), 80 °C, overnight) of the vinyl boronate followed by basic hydrogen peroxide oxidation (3 M NaOH, H_2O_2, quench with $Na_2S_2O_3$). The resulting diol was protected as the acetonide (*p*-toluenesulfonic acid and 2,2-dimethoxypropane). Racemic material was prepared from the diboration of 1-methyl-4-(propa-1,2-dienyl)benzene as described in the general procedure using tricyclohexylphosphine. Configuration was

established in comparison to authentic material prepared by Sharpless asymmetric dihydroxylation of 4-methyl-*trans*-β-methylstyrene.[48] The resulting diol was protected as the acetonide (*p*-toluenesulfonic acid and 2,2-dimethoxypropane).

Chiral GLC (β-dex, Supelco, 115 °C) -- analysis of acetonide derived from reduction and oxidation of reaction product as described above.



Diboration Product | Authentic | Racemic | Diboration Product & Racemic

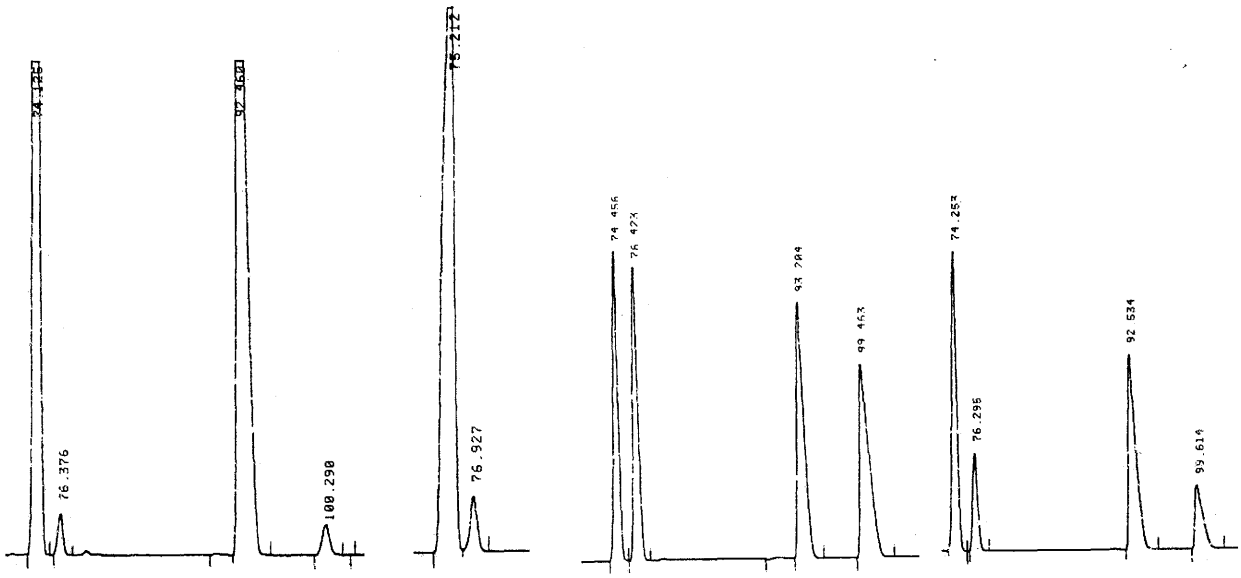


(*S*)-2-(1-(4-Methoxyphenyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 2.5, entry 9). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (6H, s, OCC**H**$_3$), 1.25 (12H, s, OCC**H**$_3$), 1.26 (6H, s, OCC**H**$_3$), 3.31 (1H, s, ArC**H**B), 3.76 (3H, s, C**H**$_3$OAr), 5.27 (1H, s, CBC**H**), 5.80 (1H, br, q, J = 1.2 Hz, CBC**H**), 6.81 (2H, d, J = 8.8 Hz, Ar**H**), 7.11 (2H, d, J = 8.4 Hz, Ar**H**). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 24.7, 24.9, 25.0, 55.1, 83.4 (2C), 83.5 (2C), 113.7, 127.7, 130.9, 132.5, 157.6. IR (neat): 3069 (m), 2965 (s), 2922 (s), 2720 (w), 2589 (w), 2546 (w), 2421 (w), 2050 (w), 1876 (w), 1658 (w), 1609 (s), 1576 (s) cm^{-1}. LRMS-(ESI+): for $C_{22}H_{35}B_2O_5$ calc'd: 401.2 $(M+H)^+$, observed: 401.2 $(M+H)^+$. Purification: silica gel with 5% ethyl acetate/hexanes provided 160.8 mg (69% yield) of a yellow oil. R_f = 0.09 (4% ethyl acetate/hexanes, stain in PMA).

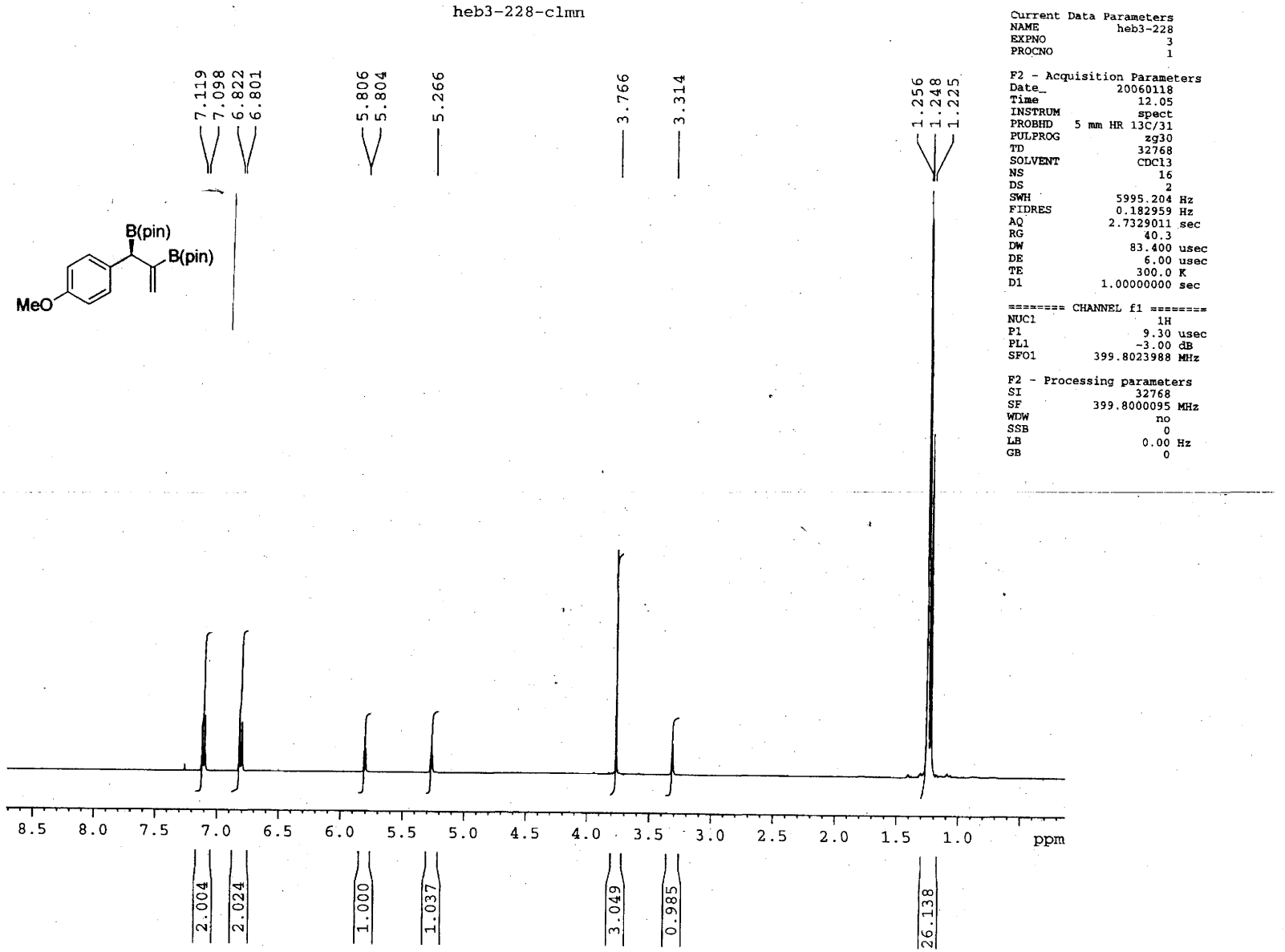
Proof of Stereochemistry. Configuration and stereoisomer ratios were determined by diimide reduction (2-nitrobenzenesulfonylhydrazide (3 equiv),[47] triethylamine (6 equiv), dioxanes (0.1 M), 80 °C, overnight) of the vinyl boronate followed by basic hydrogen peroxide oxidation (3 M NaOH, H_2O_2, quench with $Na_2S_2O_3$). The resulting diol was protected as the acetonide (*p*-toluenesulfonic acid and 2,2-dimethoxypropane). Racemic material was prepared from the diboration of 1-methoxy-4-(propa-1,2-dienyl)benzene as described in the general procedure using tricyclohexylphosphine. Configuration was established in comparison to authentic material prepared by Sharpless asymmetric

dihydroxylation of anethole.[48] The resulting diol was protected as the acetonide (*p*-toluenesulfonic acid and 2,2-dimethoxypropane).

Chiral GLC (β-dex, Supelco, 120 °C) – analysis of acetonide derived from reduction and oxidation of reaction product as described above.



Diboration Product | Authentic | Racemic | Diboration Product & Racemic



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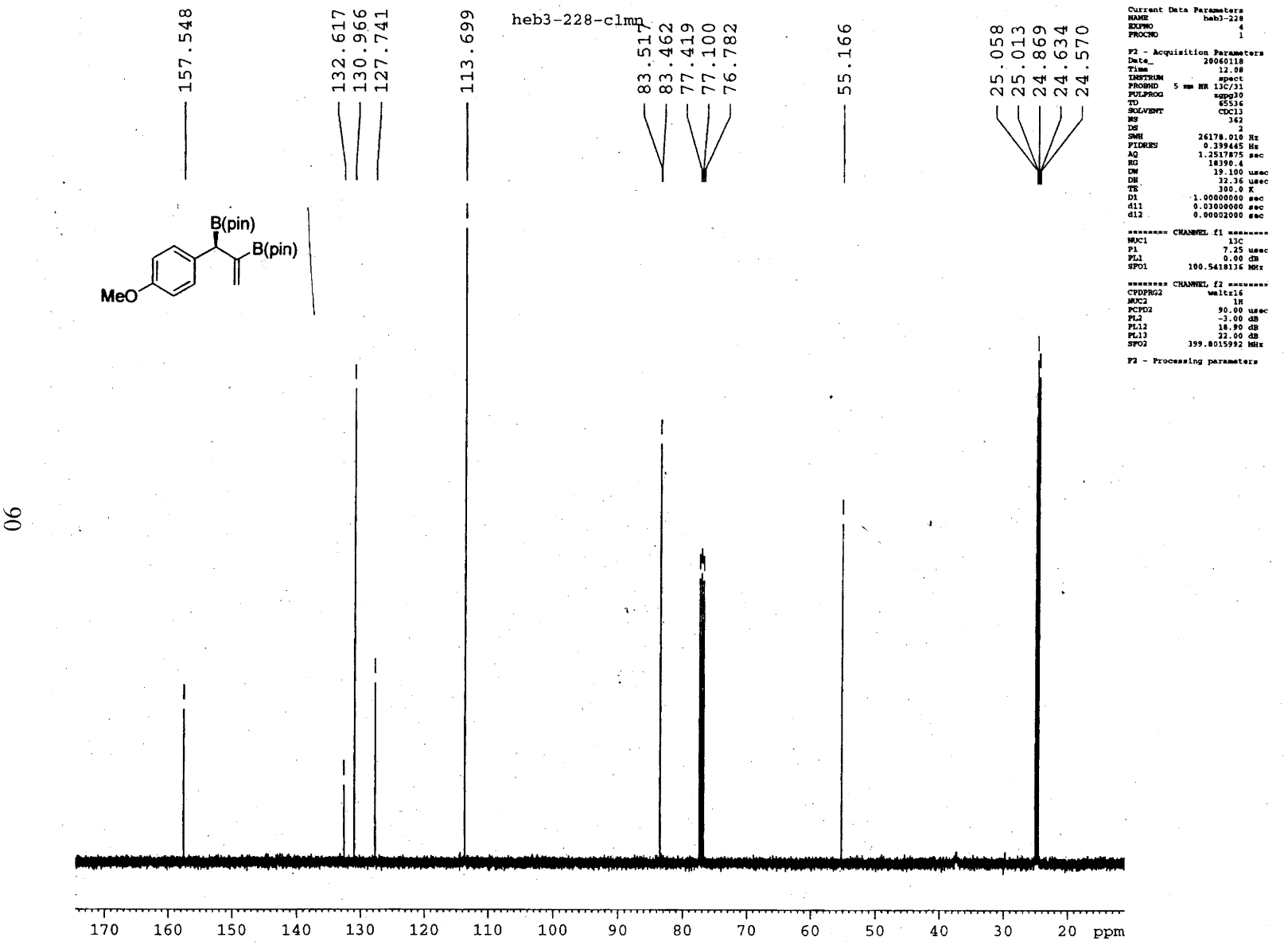
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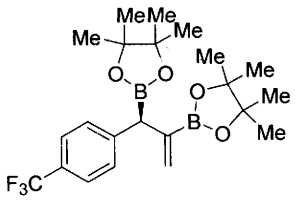
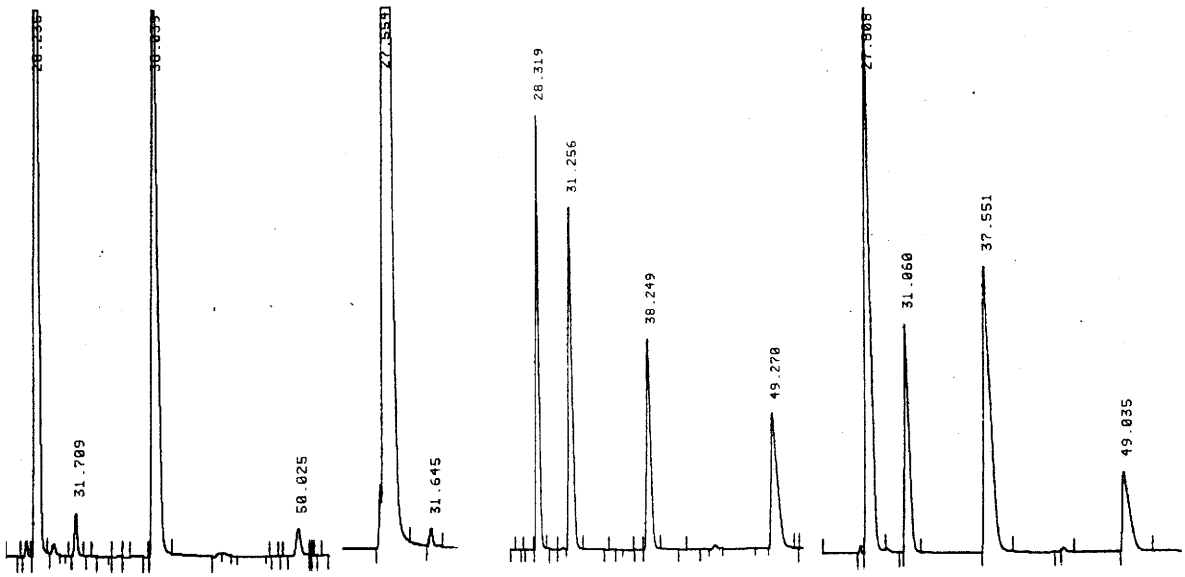


(*S*)-4,4,5,5-Tetramethyl-2-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(4-(trifluoromethyl)phenyl)prop-2-en-yl)-1,3,2-dioxaborolane (Table 2.5, entry 10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (12H, s, OCC**H**$_3$), 1.25 (12H, s, OCC**H**$_3$), 3.44 (1H, s, ArC**H**B), 5.34 (1H, s, CBC**H**), 5.86 (1H, s, CBC**H**), 7.33 (2H, d, J = 8.0 Hz, Ar**H**), 7.51 (2H, d, J = 7.5 Hz, Ar**H**). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7 (2C), 24.8 (2C), 24.9 (2C), 25.0 (2C), 83.8 (2C), 83.9 (2C), 124.6 (1C, q, $^{1}J_{CF}$ = 271 Hz), 125.1 (2C, q, $^{3}J_{CF}$ = 3.7 Hz), 127.8 (1C, q, $^{2}J_{CF}$ = 32.2 Hz), 128.9, 130.3 (2C), 145.6. ^{19}F NMR (376.4 MHz, $CDCl_3$) δ -62.8 (s). IR (neat): 2984 (s), 2930 (s), 2859 (w), 2354 (w), 1627 (m), 1366 (s), 1323 (s), 1133 (s) cm^{-1}. LRMS-(ESI+): for $C_{22}H_{31}B_2F_3O_4$ calc'd: 439.2 $(M+H)^+$, observed: 439.2 $(M+H)^+$. Purification: silica gel with 4% ethyl acetate/hexanes as the eluant afforded 104 mg (53% yield) of a yellow oil. R_f = 0.23 (4% ethyl acetate/hexanes, stain in PMA).

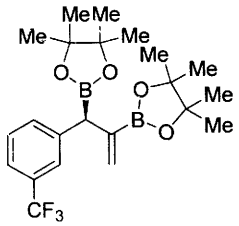
Proof of Stereochemistry. Configuration and stereoisomer ratios were determined by diimide reduction (2-nitrobenzenesulfonylhydrazide (3 equiv),[47] triethylamine (6 equiv), dioxanes (0.1 M), 80 °C, overnight) of the vinyl boronate followed by basic hydrogen peroxide oxidation (3 M NaOH, H_2O_2, quench with $Na_2S_2O_3$). The resulting diol was protected as the acetonide (*p*-toluenesulfonic acid and 2,2-dimethoxypropane). Racemic material was prepared from the diboration of 1-(propa-1,2-dienyl)-4-(trifluoromethyl)benzene as described in the general procedure using tricyclohexylphosphine. Configuration was established in comparison to authentic material prepared by Sharpless asymmetric dihydroxylation of 4-trifluoromethyl-*trans*-β-

methylstyrene.[48] The resulting diol was protected as the acetonide (*p*-toluenesulfonic acid and 2,2-dimethoxypropane).

Chiral GLC (β-dex, Supelco, 105 °C) – analysis of acetonide derived from reduction and oxidation of reaction product as described above.



Diboration Product Authentic Racemic Diboration Product & Racemic

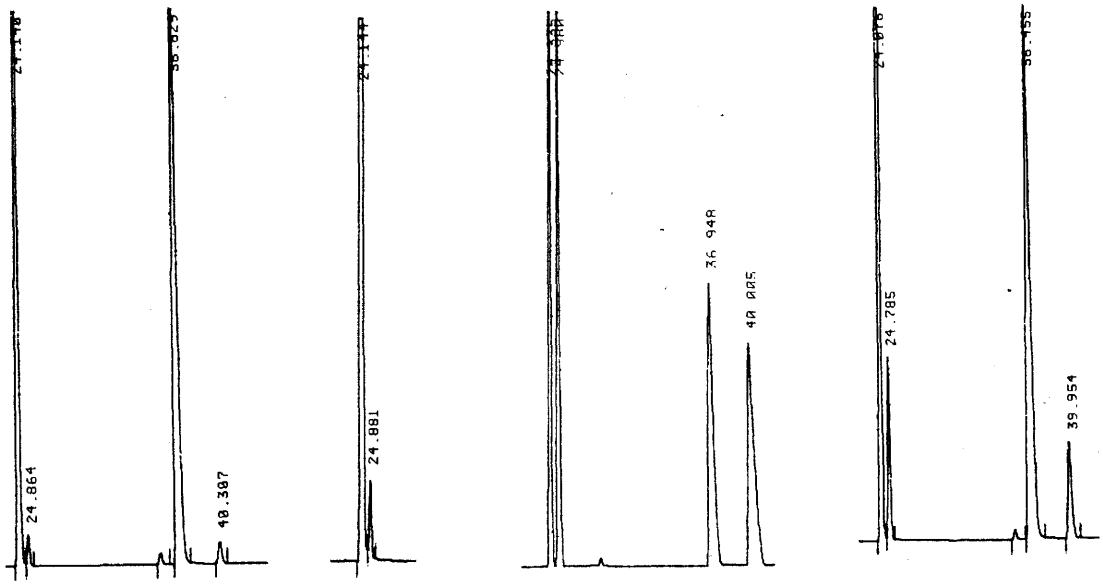


(*S*)-4,4,5,5-Tetramethyl-2-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(3-trifluoromethyl)phenyl)prop-2-en-2-yl)-1,3,2-dioxaborolane (Table 2.5, entry 11). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (6H, s, OCC**H**$_3$), 1.24 (6H, s, OCC**H**$_3$), 1.25 (6H, s, OCC**H**$_3$), 1.26 (6H, s, OCC**H**$_3$), 3.42 (1H, s, ArC**H**B), 5.33 (1H, s, CBC**H**), 5.85 (1H, s, CBC**H**), 7.36-7.42 (3H, m, Ar**H**), 7.53 (1H, s, *o*-Ar**H**). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6 (2C), 24.7 (2C), 24.9 (2C), 25.0 (2C), 83.8 (2C), 83.9 (2C), 122.4 (1C, q, $^{3}J_{CF}$ = 3.8 Hz), 124.6 (1C, q, $^{1}J_{CF}$ = 272.3 Hz), 126.9 (1C, q, $^{3}J_{CF}$ = 3.8 Hz), 128.6, 128.9, 130.4 (1C, q, $^{2}J_{CF}$ = 32.2 Hz), 133.5, 142.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.1. IR (neat): 3064 (w), 2978 (s), 2932 (s), 2357 (w), 1603 (m), 1445 (m), 1366 (s), 1320 (s) cm^{-1}. LRMS-(ESI+): For $C_{22}H_{31}B_2F_3O_4$ calc'd: 439.2 $(M+H)^+$, observed: 439.2 $(M+H)^+$. Purification: silica gel with 4% ethyl acetate/hexanes delivered 97 mg (50% yield) of a yellow oil. R_f = 0.18 (4% ethyl acetate/hexanes, stain in PMA).

Proof of Stereochemistry. Configuration and stereoisomer ratios were determined by diimide reduction (2-nitrobenzenesulfonylhydrazide (3 equiv),[47] triethylamine (6 equiv), dioxanes (0.1 M), 80 °C, overnight) of the vinyl boronate followed by basic hydrogen peroxide oxidation (3 M NaOH, H_2O_2, quench with $Na_2S_2O_3$). The resulting diol was protected as the acetonide (*p*-toluenesulfonic acid and 2,2-dimethoxypropane). Racemic material was prepared from the diboration of 1-(propa-1,2-dienyl)-3-(trifluoromethyl)benzene as described in the general procedure using tricyclohexylphosphine. Configuration was established in comparison to authentic

material prepared by Sharpless asymmetric dihydroxylation of 3-trifluoromethyl-*trans*-β-methylstyrene.[48] The resulting diol was protected as the acetonide (*p*-toluenesulfonic acid and 2,2-dimethoxypropane).

Chiral GLC (β-dex, Supelco, 100 °C) – analysis of acetonide derived from reduction and oxidation of reaction product as described above.



Diboration Product | Authentic | Racemic | Diboration Product & Racemic

2.5.5. Preparation of Rhodium Complexes for Analysis by IR.[24]

Chlorocarbonylbis(triphenylphosphine)rhodium and chlorocarbonylbis(tricyclohexylphosphine)rhodium were prepared according to literature procedure and spectral data and analysis of the complexes by MALDI are in accordance with the literature.[24]

2.5.5.1. Preparation of trans-[(R,R)-2.4]$_2$Rh(CO)Cl. In the dry box, a 25-mL round-bottom flask was charged with chlorodicarbonylrhodium(I) dimer (80 mg, 0.2057 mmol). To a separate 25-mL pear shaped flask was added (*R,R*)-TADDOLPNMe$_2$ **(*R,R*)-2.4** (444.1 mg, 0.8231 mmol). Both flasks were sealed with septa and removed from the glove box. Chlorodicarbonylrhodium(I) dimer and **(*R,R*)-2.4** were dissolved in anhydrous benzene (1 and 5 mL, respectively). Mild heating was required to dissolve **(*R,R*)-2.4**. The solution of **(*R,R*)-2.4** was transferred by cannula into chlorodicarbonylrhodium(I) dimer solution; CO evolution was immediate. The reaction mixture stirred at room temperature for 30 min, when solvent was removed on the rotary evaporator. Residual solvent was removed *in vacuo* overnight to afford 473.6 mg (93% yield) of a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.49 (6H, s, $(CH_3)_2$), 0.58 (6H, s, $(CH_3)_2$), 2.23 (12H, t, J = 5.2 Hz, 2 x $(N(CH_3)_2)$), 5.42 (2H, d, J = 8.0 Hz, OCH), 5.49 (2H, d, J = 8.0 Hz, OCH), 7.16-7.36 (28H, m, ArH), 7.45 (4H, t, J = 7.7 Hz, ArH). 7.54-7.56 (4H, m, ArH), 7.70-7.72 (4H, m, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.6 (2C), 26.9 (2C), 38.5 (4C, t, J_{CP} = 5.6 Hz), 79.3 (2C), 79.5 (2C), 87.2 (2C), 88.1 (2C), 115.1 (2C), 126.8 (2C), 126.9

(4C), 127.2 (4C), 127.4 (4C), 127.7 (2C), 17.9 (2C), 128.0 (4C), 128.3 (4C), 128.4 (2C), 128.7 (4C), 129.0 (4C), 129.3 (4C). ^{31}P NMR (202 MHz, $CDCl_3$) δ 117.6, 118.6. IR (CH_2Cl_2): 1982 (s), 1607 (s), 1491 (m) cm^{-1}. MALDI-TOF with CAA overlay for $C_{66}H_{68}N_2O_8P_2Rh$ calc'd: 1181.35 $(M\text{-}CO\text{-}Cl)^+$, observed: 1181.488 $(M\text{-}CO\text{-}Cl)^+$.

2.5.5.2. Preparation of trans-[(R,R)-2.17]$_2$Rh(CO)Cl. In the dry box, a 25-mL round-bottom flask was charged with chlorodicarbonylrhodium(I) dimer (30 mg, 0.0771 mmol). To a separate 25-mL pear shaped flask was added (*R,R*)-xylylTADDOLPNMe$_2$ **(*R,R*)-2.17** (201.1 mg, 0.3086 mmol). Both flasks were sealed with septa and removed from the glove box. Chlorodicarbonylrhodium(I) dimer and **(*R,R*)-2.17** were dissolved in anhydrous benzene (1 mL). The solution of **(*R,R*)-2.17** was transferred by cannula into the chlorodicarbonylrhodium(I) dimer solution; CO evolution was immediate. The reaction mixture was stirred at room temperature for 5 min after which when solvent was removed on the rotary evaporator. Residual solvent was removed *in vacuo* overnight and the unpurified reaction mixture was recrystallized from pentanes to afford 114 mg (50% yield) of a yellow solid.

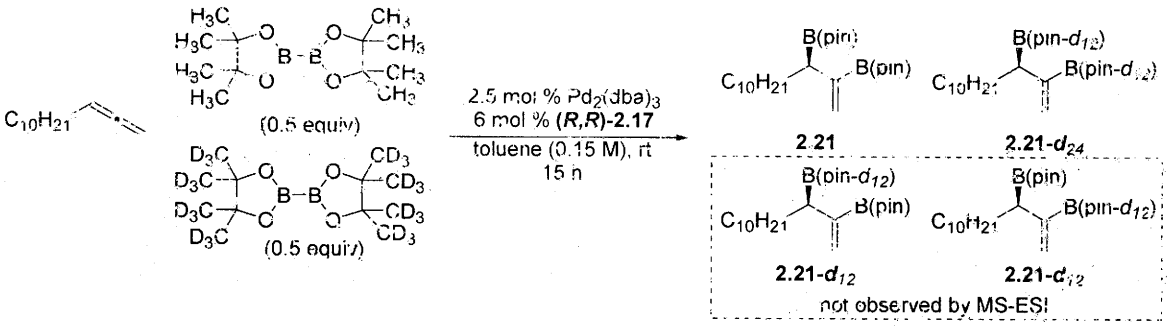
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.44 (6H, s, $(CH_3)_2$), 0.54 (6H, s, $(CH_3)_2$), 2.04 (12H, t, J = 5.2 Hz, 2 x $(N(CH_3)_2)$, 2.21 (24H, s, Ar-CH_3), 2.25 (12H, s, Ar-CH_3), 2.42 (12H, s, Ar-CH_3), 5.26 (2H, d, J = 7.5 Hz, OC**H**), 5.64 (2H, d, J = 8.0 Hz, OC**H**), 6.80 (2H, s, Ar**H**), 6.82 (2H, s, Ar**H**), 6.85 (2H, s, Ar**H**), 6.90 (4H, s, Ar**H**), 6.94 (2H, s, Ar**H**), 7.07 (4H, s, Ar**H**), 7.10 (4H, s, Ar**H**), 7.18 (4H, s, Ar**H**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5 (4C), 21.6 (4C), 21.7 (4C), 21.8 (4C), 26.5 (2C), 27.0 (2C), 38.2 (4C, t, J = 6.3 Hz), 78.2

(2C), 79.7 (2C), 88.4 (2C), 86.7 (2C), 115.1 (2C), 125.3 (2C), 126.9 (4C), 127.2 (6C), 128.5 (2C), 128.6 (2C), 129.3 (4C), 129.7 (4C), 135.5 (4C), 135.9 (4C), 137.0 (4C), 137.1 (4C), 141.7 (2C), 142.3 (2C), 143.0 (2C), 144.9 (2C). ^{31}P NMR (202 MHz, $CDCl_3$) δ 116.5, 117.5. MALDI-TOF with CAA overlay for $C_{82}H_{100}N_2O_8P_2Rh$ calc'd: 1405.601 $(M\text{-}CO\text{-}Cl)^+$, observed: 1405.778 $(M\text{-}CO\text{-}Cl)^+$.

2.5.6. Crossover Experiment

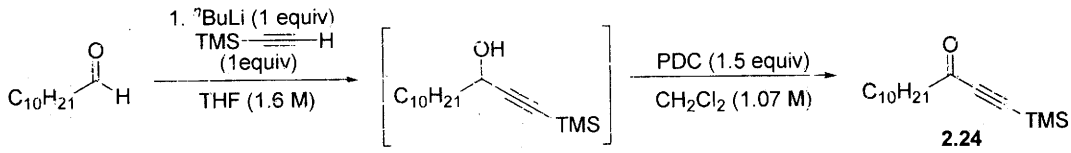
2.5.6.1. Preparation of Pinacol-d_{12}.[29] To a 1-L 2-neck flask equipped with a magnetic stir bar was added flame-dried magnesium turnings (3.08 g, 127 mmol). Under nitrogen, mercury(II) chloride (3.45 g, 12.71 mmol) was added, followed by benzene (500 mL, 0.025 M). The flask was charged with acetone-d_6 (65.5 mL, 890 mmol) and the resulting mixture was stirred under nitrogen for 24 h at 60 °C. The mixture was cooled to ambient temperature, quenched with distilled water (200 mL) and stirred at 60 °C for an additional 3 h. The suspension was extracted with diethyl ether and the organic layers were combined and filtered on a Büchner funnel. The solvent was removed by distillation to provide a yellow oil which was purified on silica gel (30% ethyl acetate/hexanes) to afford 2.27 g (13% yield) of a clear oil. Spectral data are in accordance with those in the literature.

2.5.6.2. Preparation of **B_2(pin-d_{12})$_2$** was prepared according to literature procedure without deviation.[29]



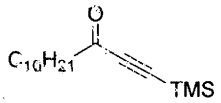
2.5.6.3. Procedure for Crossover Experiment. In the dry box, a 6-dram vial with a magnetic stir bar was charged with $Pd_2(dba)_3$ (7.6 mg, 8.3 μmol), **(*R,R*)-2.17**, 13.2 mg, 19.9 μmol), and toluene (2.21 mL, 0.15 M). The metal and ligand were complexed for 1 h, at which time $B_2(pin)_2$ (43.2 mg, 0.170 mmol) and $B_2(pin\text{-}d_{12})_2$ (46.3 mg, 0.166 mmol) were added simultaneously to the reaction mixture. Tridec-1,2-diene (60.3 mg, 0.332 mmol) was then added and the vial was sealed with a polypropylene cap and electrical tape, and then removed from the dry box. The reaction was stirred at room temperature for 15 h when it was concentrated to dryness. Residual solvent was removed *in vacuo* and the material was purified by passage through a short column of silica gel (5% ethyl acetate/hexanes). All fractions were pooled, concentrated, and submitted for LRMS-ESI$^+$ for $C_{25}H_{48}B_2O_4$: calc'd: 435.3 $(M+H)^+$, observed: 435.3 $(M+H)^+$ For $C_{25}H_{25}D_{24}B_2O_4$: calc'd: 459.5 $(M+H)^+$, observed: 459.5 $(M+H)^+$. $C_{25}H_{36}D_{12}B_2O_4$ was not observed.

2.5.7. Synthesis of (*R*)-2.23-d_1



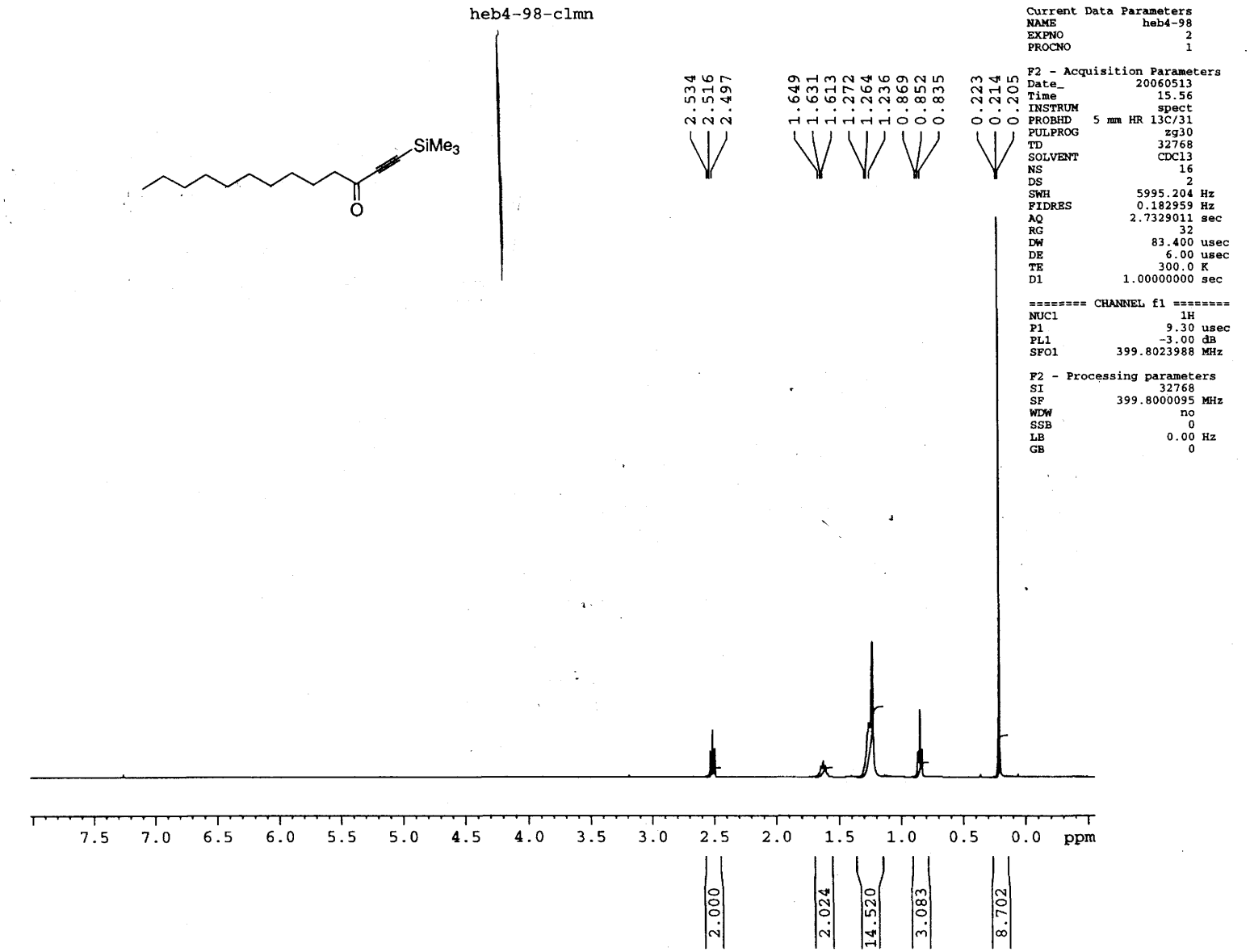
1-(Trimethylsilyl)tridec-1-yn-3-one 2.24.[30] To a 25-mL round-bottom flask equipped with magnetic stir bar and sealed with a septum, was added trimethylsilylacetylene (1 mL, 7.07 mmol) and THF (4.4 mL). The flask was cooled to 0 °C (ice-water bath) and charged with 1.54 M ^{n}BuLi (4.59 mL). After stirring for 30 min at 0 °C, undecanal was added slowly over 30 min and the reaction was allowed to stir at 0 °C for an additional 60 min. The reaction was quenched with water (10 mL) and extracted with ethyl acetate (3 times). The organic layers were combined, washed with 0.5 M hydrogen chloride, saturated sodium bicarbonate, and brine. Organic extracts were dried ($MgSO_4$), filtered, and concentrated on a rotary evaporator to afford 1-trimethylsilanyl-tri-dec-1-yl-ol which was immediately used in the next step.

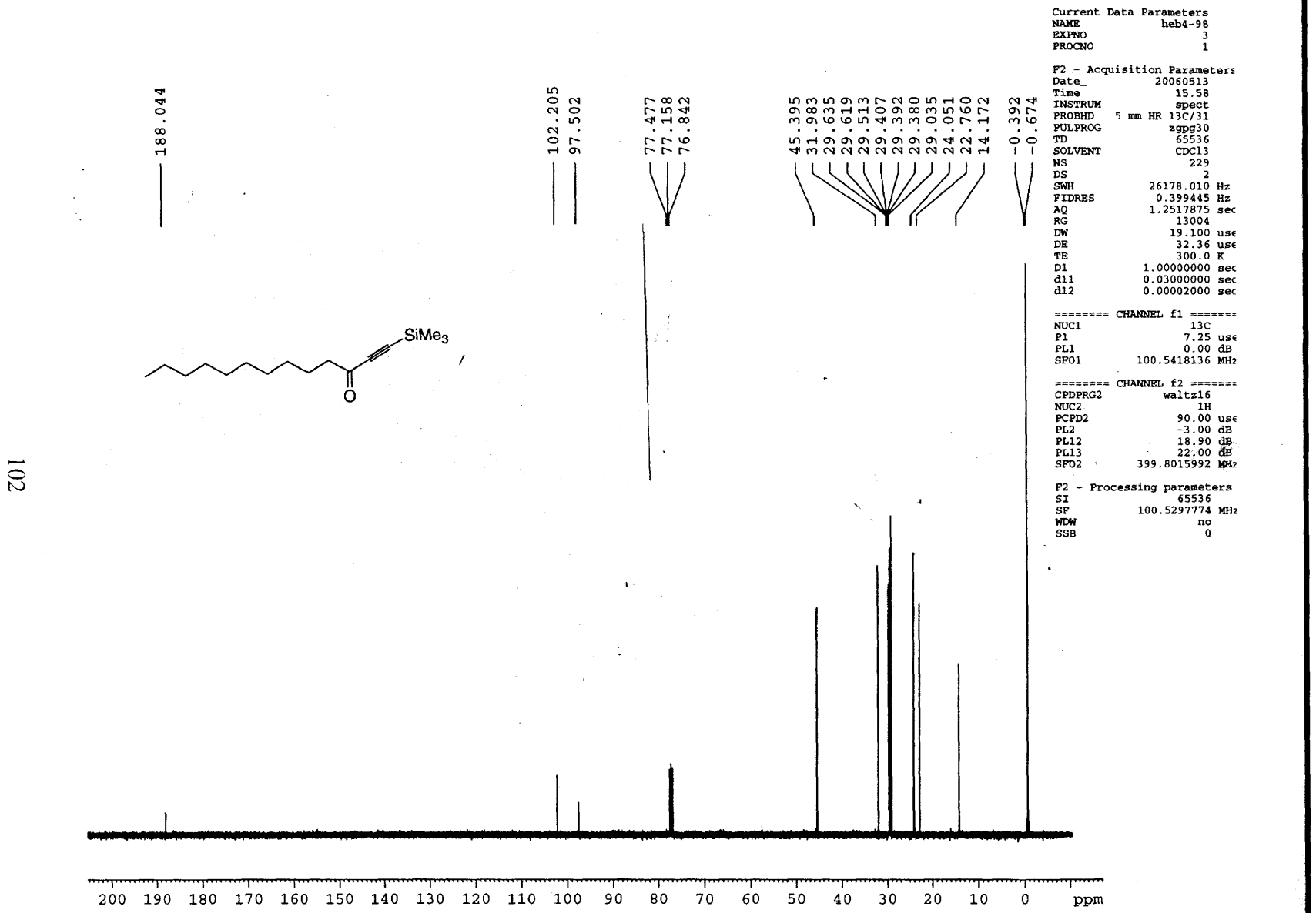
PDC Oxidation: To a septum-sealed 100-mL round-bottom flask with a magnetic stir bar and 4Å MS (1.27 g) was added CH_2Cl_2 (10 mL, 1.07 M) and pyridinium dichromate (3.98 g). In a separate flask, the unpurified material from above was dissolved in CH_2Cl_2 (4.4 mL) and transferred by cannula into the reaction flask. After the reaction stirred for 16 h, it was diluted with diethyl ether and filtered over Celite. The filtrate was concentrated to afford a clear oil, which was purified by silica gel chromatography (2% ethyl acetate/hexanes) affording 1.17 g (62% yield) of a clear oil.



2.24

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.24 (9H, s, $(\mathbf{CH_3})_3Si$), 0.85 (3H, t, J = 6.8 Hz, $\mathbf{CH_3}CH_2$), 1.24-1.27 (14H, m, br, $(\mathbf{CH_2})_7$), 1.63 (2H, t, J = 7.2 Hz, $\mathbf{CH_2}CH_2CO$), 2.52 (2H, t, J = 7.4 Hz, $CH_2\mathbf{CH_2}CO$). ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.67 (3C), 14.2, 22.8, 24.0, 29.0, 29.4, 29.5, 29.6, 31.9, 97.5, 102.2, 188.0. IR (neat): 2942 (s), 2843 (s), 2148 (m), 2089 (w), 1681 (s), 1459 (s), 1404 (w), 1241 (s) cm^{-1}. LRMS-(ESI+): for $C_{16}H_{30}NaOSi$ calc'd: 289.2 $(M+Na)^+$, observed: 289.3 $(M+Na)^+$. Purification: silica gel with 2% ethyl acetate/hexanes as the eluant afforded 1.17 g (62% yield) of a clear oil. R_f = 0.45 (10% ethyl acetate/hexanes, stain in PMA)


heb4-98-clmn
SiMe3
O
2.534
2.516
2.497
1.649
1.631
1.613
1.272
1.264
1.236
0.869
0.852
0.835
0.223
0.214
0.205
Current Data Parameters
NAME heb4-98
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060513
Time 15.56
INSTRUM spect
PROBHD 5 mm HR 13C/31
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 32
DW 83.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 9.30 usec
PL1 -3.00 dB
SFO1 399.8023988 MHz
F2 - Processing parameters
SI 32768
SF 399.8000095 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.000
2.024
14.520
3.083
8.702


188.044
102.205
97.502
77.477
77.158
76.842
45.395
31.983
29.635
29.619
29.513
29.407
29.392
29.380
29.035
24.051
22.760
14.172
-0.392
-0.674
SiMe3
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm
Current Data Parameters
NAME heb4-98
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
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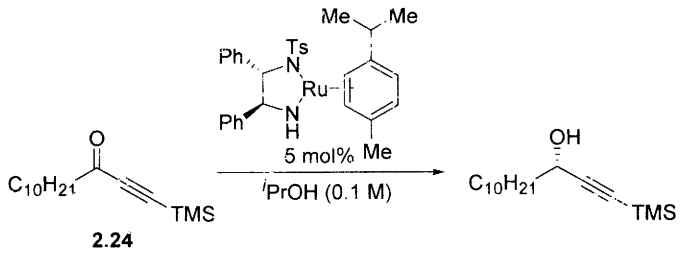
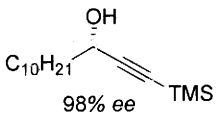
INSTRUM spect
PROBHD 5 mm HR 13C/31
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 229
DS 2
SWH 26178.010 Hz
FIDRES 0.399445 Hz
AQ 1.2517875 sec
RG 13004
DW 19.100 use
DE 32.36 use
TE 300.0 K
D1 1.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
======== CHANNEL f1 =======
NUC1 13C
P1 7.25 use
PL1 0.00 dB
SFO1 100.5418136 MHz
======== CHANNEL f2 =======
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 use
PL2 -3.00 dB
PL12 18.90 dB
PL13 22.00 dB
SFO2 399.8015992 MHz
F2 - Processing parameters
SI 65536
SF 100.5297774 MHz
WDW no
SSB 0



2.24

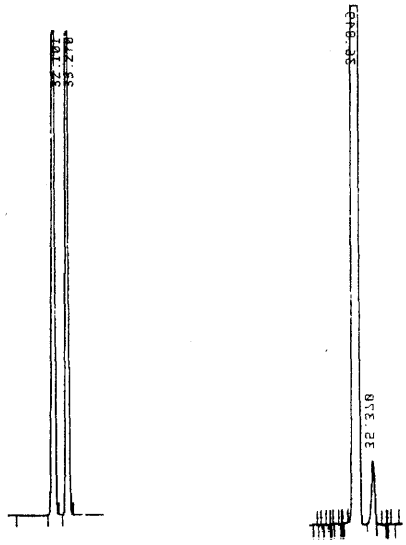
(S)-1-(Trimethylsilyl)tridec-1-yn-3-ol.[31] To a 100-mL round-bottom flask with magnetic stir bar was added 1-(trimethylsilyl)-tridec-1-yn-3-one (1 g, 3.76 mmol) in isopropanol (37.6 mL). Next, Ru[(1*S*,2*S*)-*p*-TsNCH(C_6H_5)CH(C_6H_5)NH](η^6-*p*-cymene) (112.6 mg, 0.187) was added. The reaction was stirred for 16 h after which time the unpurified reaction mixture was concentrated, and purified on silica gel to afford 1.00 g (91% yield, 98% *ee*) of a clear oil.



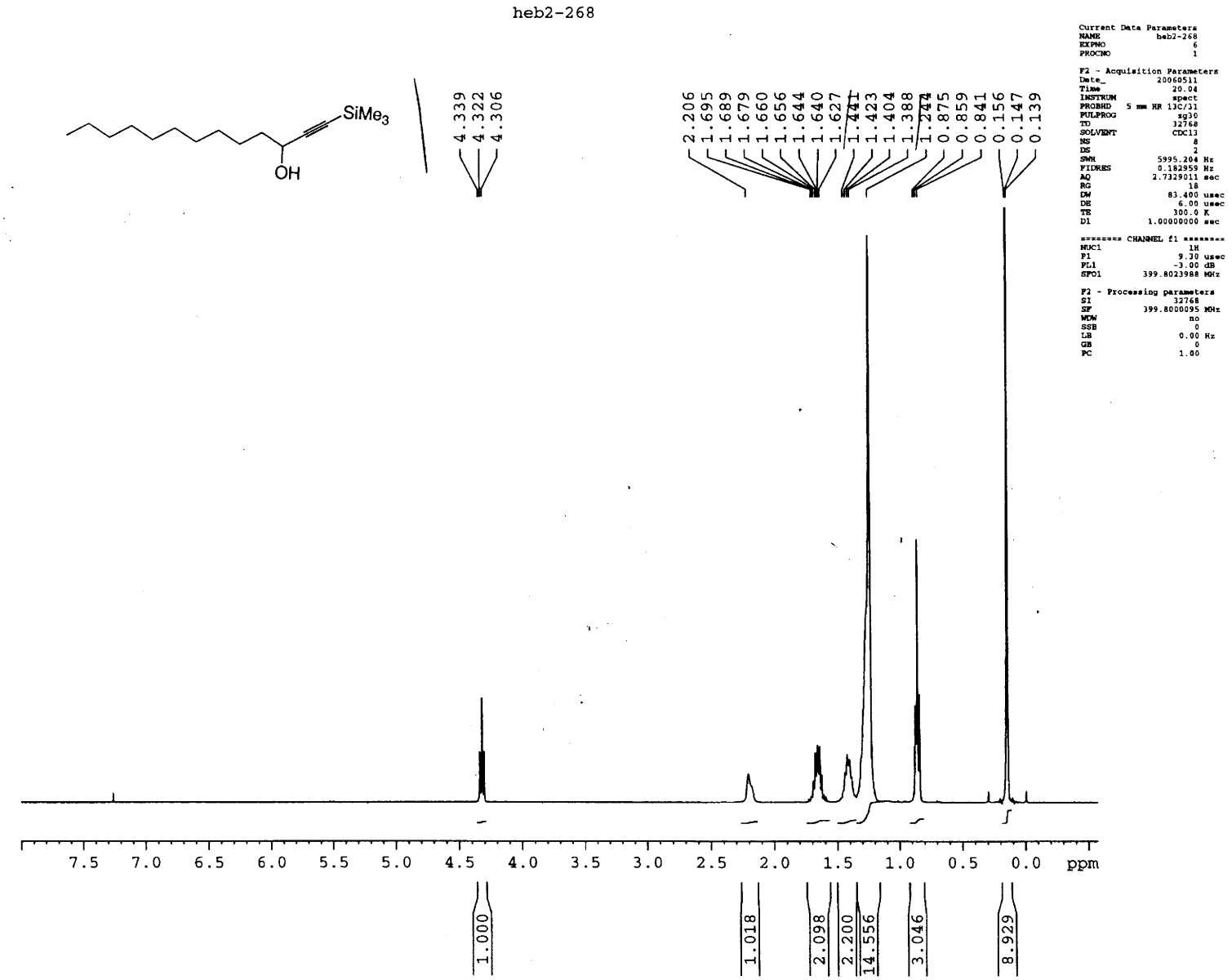
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (9H, s, Si($C\mathbf{H_3}$)$_3$), 0.86 (3H, t, J = 6.7 Hz, $C\mathbf{H_3}CH_2CH_2$), 1.24 (14 H, s, br, ($C\mathbf{H_2}$)$_7$), 1.38-1.44 (2H, m, $C\mathbf{H_2}CH_2CHOH$), 1.63-1.69 (2H, m, $CH_2C\mathbf{H_2}CHOH$), 2.20 (1H, s br, O**H**), 4.32 (1H, t, J = 6.6 Hz, C**H**OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.008 (3C), 14.2, 22.8, 25.2, 29.3, 29.4, 29.6, 29.7, 29.8, 32.0, 37.8, 62.9, 89.2, 107.2. IR (neat): 3315 (s), 2935 (s), 2859 (s), 2164 (s), 1453 (s), 1399 (m), 1252 (s) cm^{-1}. LRMS-(ESI+): for $C_{16}H_{31}NaOSi$ calc'd: 290.2042 $(M+Na)^+$, observed: 291.3 $(M+Na)^+$. Purification: silica gel with 5% ethyl acetate/hexanes as the eluant provided 1.00 g (91% yield, 98% *ee*) of a clear oil. R_f = 0.45 (10% ethyl acetate/hexanes, stain in PMA).

Determination of Enantioselectivity. The trimethylsilyl group of (*S*)-1-(trimethylsilyl)tridec-1-yn-3-ol was deprotected with potassium carbonate (1 equiv) in methanol (1.0 M). The hydroxyl group was then protected using acetic anhydride (1.2 equiv), triethylamine (3 equiv), and 4-dimethylaminopyridine (cat.) in dichloromethane (0.25 M). The enantiomerically enriched material was compared to racemic product.

Chiral GLC (β-dex, Supelco, 140 °C) -- analysis of acetate derived from TMS deprotection and alcohol protection of the reaction product as described above.



Racemic Chiral Propargyl Acetate


heb2-268
SiMe3
OH
4.339
4.322
4.306
2.206
1.695
1.689
1.679
1.660
1.656
1.644
1.640
1.627
1.441
1.423
1.404
1.388
1.244
0.875
0.859
0.841
0.156
0.147
0.139
Current Data Parameters
NAME heb2-268
EXPNO 6
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060511
Time 20.04
INSTRUM spect
PROBHD 5 mm HR 13C/31
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 18
DW 83.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 9.30 usec
PL1 -3.00 dB
SFO1 399.8023988 MHz
F2 - Processing parameters
SI 32768
SF 399.8000095 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
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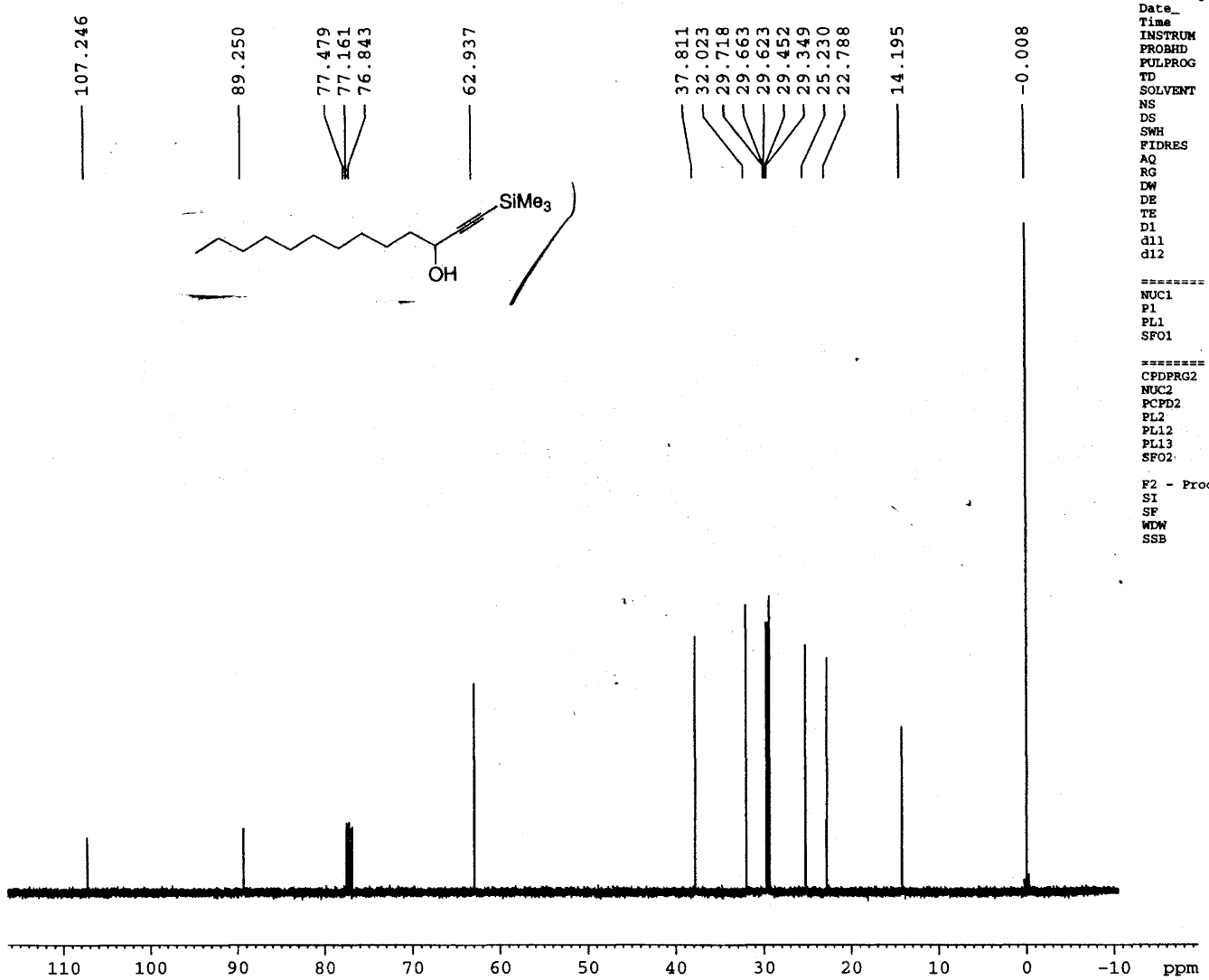
1.018
2.098
2.200
14.556
3.046
8.929



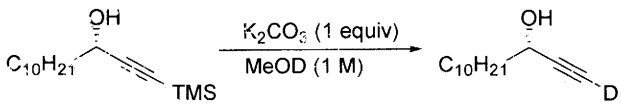
Current Data Parameters
NAME heb2-268
EXPNO 7
PROCNO 1

F2 - Acquisition Parameters
Date_ 20060511
Time 20.06
INSTRUM spect
PROBHD 5 mm HR 13C/31
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 110
DS 2
SWH 26178.010 Hz
FIDRES 0.399445 Hz
AQ 1.2517875 sec
RG 13004
DW 19.100 use
DE 32.36 use
TE 300.0 K
D1 1.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec

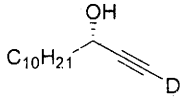
======== CHANNEL f1 =======
NUC1 13C
P1 7.25 use
PL1 0.00 dB
SFO1 100.5418136 MHz

======== CHANNEL f2 =======
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 use
PL2 -3.00 dB
PL12 18.90 dB
PL13 22.00 dB
SFO2 399.8015992 MHz

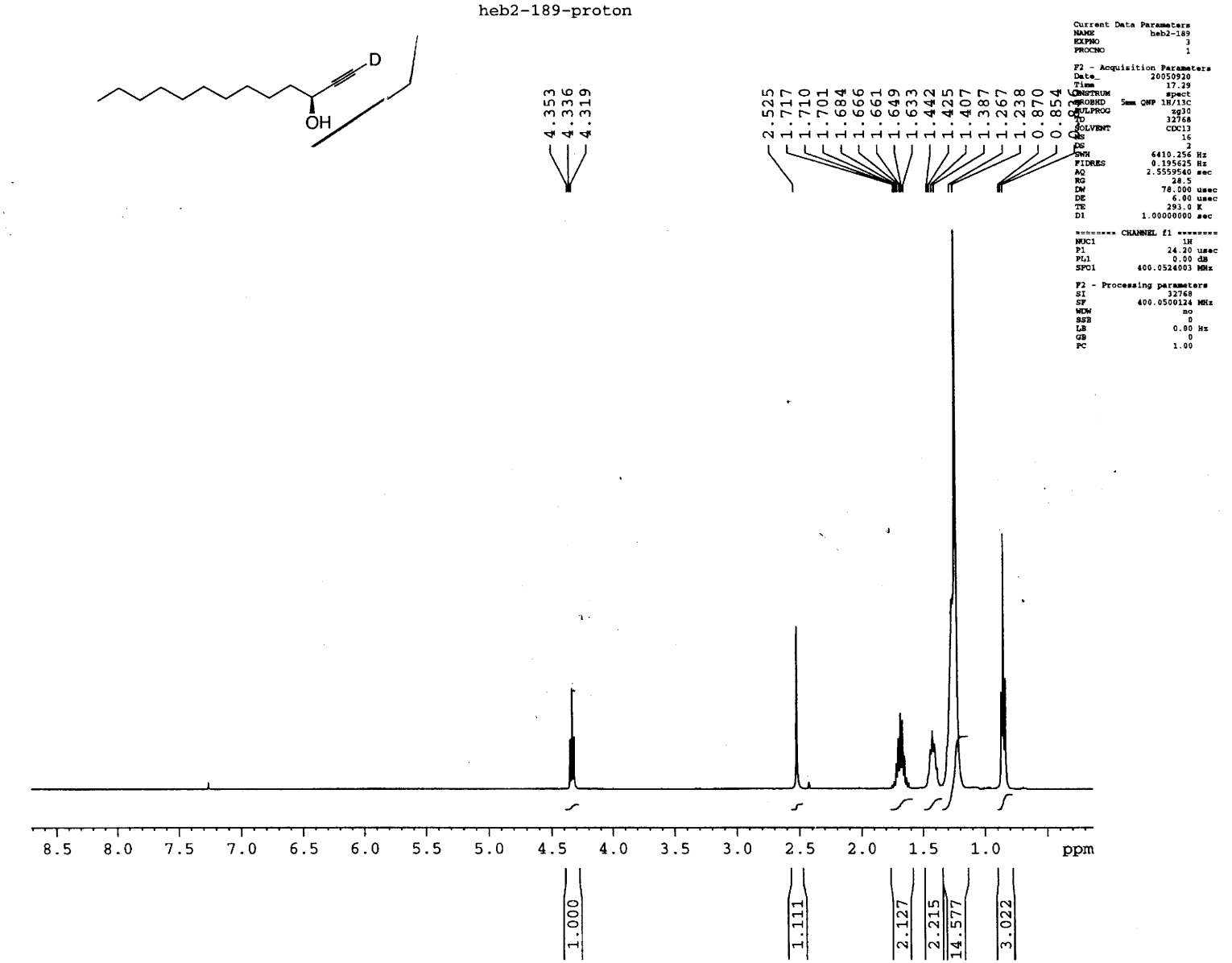
F2 - Processing parameters
SI 65536
SF 100.5297770 MHz
WDW no
SSB 0

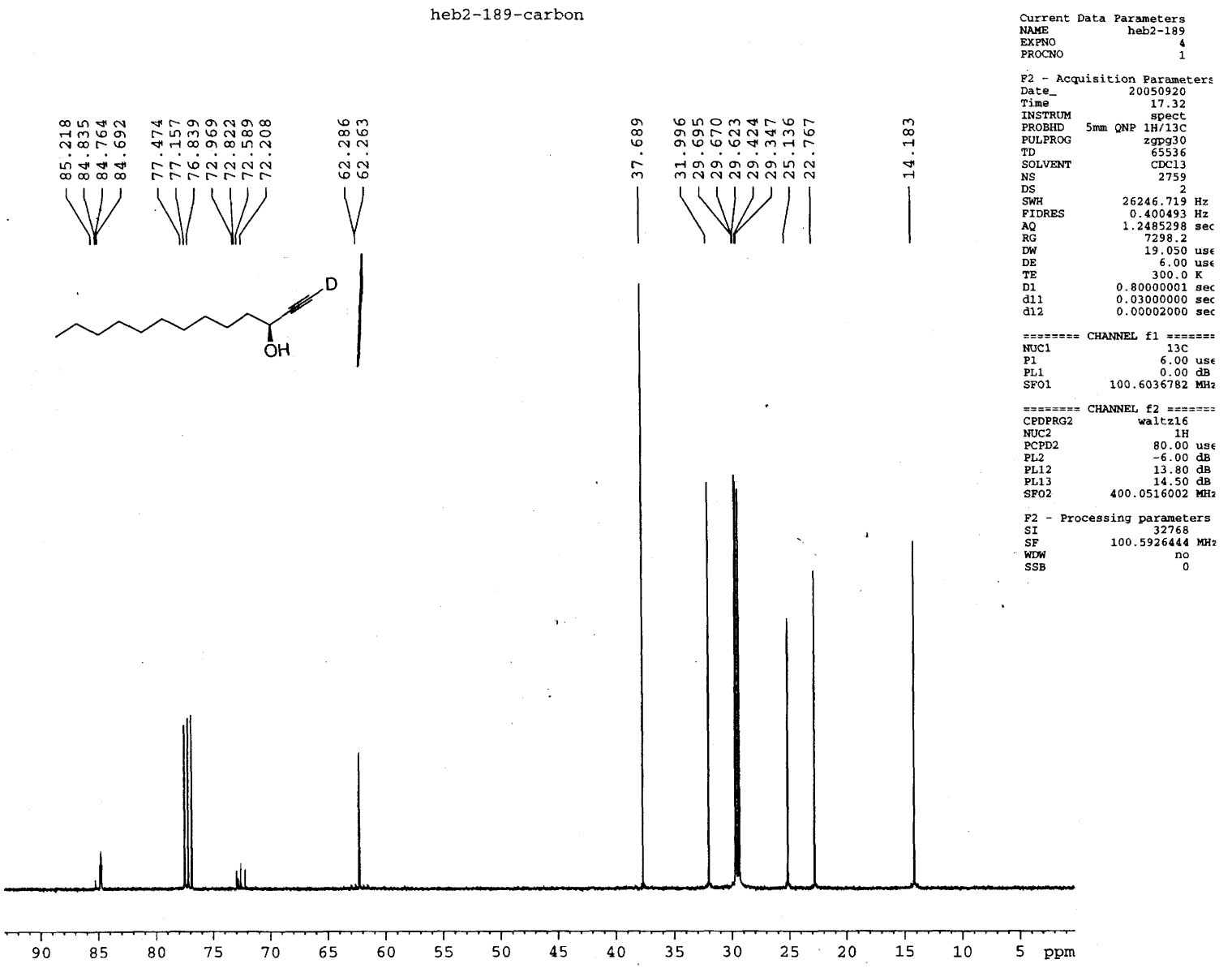


(*S*)-1-Deuteriotridec-1-yn-3-ol.[31] To a 50-mL round-bottom flask with magnetic stir bar, was added (*S*)-1-(trimethylsilyl)tridec-1-yn-3-ol (2.23 g, 8.31 mmol) in methanol-OD (8.3 mL). Potassium carbonate (anhydrous) (1.13 g, 8.31 mmol) was added under nitrogen. After the reaction stirred for 3 h, it was quenched with water and diluted with ethyl acetate. The aqueous layer was washed twice with ethyl acetate, then the organic extracts were combined and washed with brine and dried ($MgSO_4$). The organic layer was filtered over Celite and concentrated on a rotary evaporator. The reaction mixture was purified on silica gel (10% ethyl acetate/hexanes) to afford 1.54 g (94% yield) of a white solid.



^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (3H, t, J = 6.8 Hz, C**H**$_3$CH$_2$), 1.24 (14H, m, (C**H**$_2$)$_7$), 1.42 (2H, m, C**H**$_2$CH$_2$CHOH), 1.68 (2H, m, CH$_2$C**H**$_2$CHOH), 2.53 (1H, s, O**H**), 4.34 (1H, t, J = 6.8 Hz, CH$_2$C**H**OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.8, 25.1, 29.3, 29.4, 29.6, 29.7, 29.8, 31.9, 37.7, 62.3 (1C, $^3J_{CD}$ = 2.3 Hz), 72.6 (1C, $^1J_{CD}$ = 38.1 Hz), 84.8 (1C, $^2J_{CD}$ = 7.2 Hz). ^{2}H NMR (61.4 MHz, $CHCl_3$) δ 2.45 (1D, s, CC**D**). IR (CH_2Cl_2): 3364 (s), 2952 (s), 2843 (s), 2593 (s), 1980 (s), 1632 (w), 1464 (s) cm^{-1}. LRMS-(ESI+) for $C_{13}H_{23}DNaO$ calc'd 220.1 $(M+Na)^+$, observed 220.1 $(M+Na)^+$. Purification: silica gel with 10% ethyl acetate/hexanes afforded 1.54 g (94% yield) of a white solid. R_f = 0.21 (10% ethyl acetate/hexanes, stain in PMA).


heb2-189-proton
D
OH
4.353
4.336
4.319
2.525
1.717
1.710
1.701
1.684
1.666
1.661
1.649
1.633
1.442
1.425
1.407
1.387
1.267
1.238
0.870
0.854
Current Data Parameters
NAME heb2-189
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050920
Time 17.29
INSTRUM spect
PROBHD 5mm QNP 1H/13C
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6410.256 Hz
FIDRES 0.195625 Hz
AQ 2.5559540 sec
RG 28.5
DW 78.000 usec
DE 6.00 usec
TE 293.0 K
D1 1.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 24.20 usec
PL1 0.00 dB
SFO1 400.0524003 MHz
F2 - Processing parameters
SI 32768
SF 400.0500124 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.000
1.111
2.127
2.215
14.577
3.022



Current Data Parameters

NAME	heb2-189
EXPNO	4
PROCNO	1

F2 - Acquisition Parameters

Date_	20050920
Time	17.32
INSTRUM	spect
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PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	2759
DS	2
SWH	26246.719 Hz
FIDRES	0.400493 Hz
AQ	1.2485298 sec
RG	7298.2
DW	19.050 use
DE	6.00 use
TE	300.0 K
D1	0.80000001 sec
d11	0.03000000 sec
d12	0.00002000 sec

======== CHANNEL f1 =======

NUC1	13C
P1	6.00 use
PL1	0.00 dB
SFO1	100.6036782 MHz

======== CHANNEL f2 =======

CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 use
PL2	-6.00 dB
PL12	13.80 dB
PL13	14.50 dB
SFO2	400.0516002 MHz

F2 - Processing parameters

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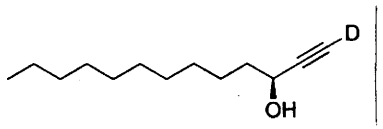
SF	100.5926444 MHz
WDW	no
SSB	0

deuterium

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Current Data Parameters
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EXPNO                       5
PROCNO                      1

F2 - Acquisition Parameters
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PROBHD   5mm QNP 1H/13C
PULPROG               zg2h
TD                    4096
SOLVENT               CDCl3
NS                       8
DS                       2
SWH                913.743 Hz
FIDRES           0.223082 Hz
AQ               2.2419283 sec
RG                     512
DW                 547.200 usec
DE                   6.00 usec
TE                  293.0 K
D1              1.00000000 sec
d11             0.03000000 sec
D20             0.20000000 sec

======== CHANNEL f1 ========
NUC1                    2H
P1                 400.00 usec
PL1                 -3.00 dB
SFO1           61.4105050 MHz

F2 - Processing parameters
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SF             61.4100502 MHz
WDW                       no
SSB                        0
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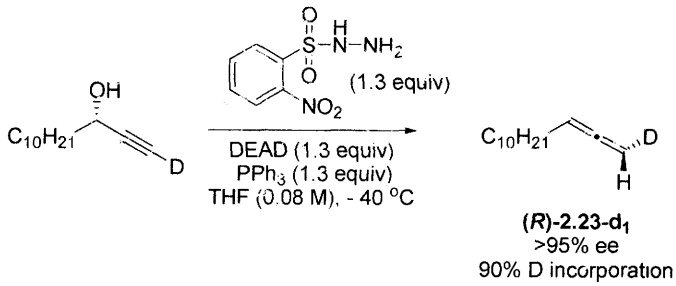
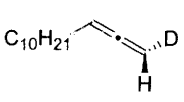


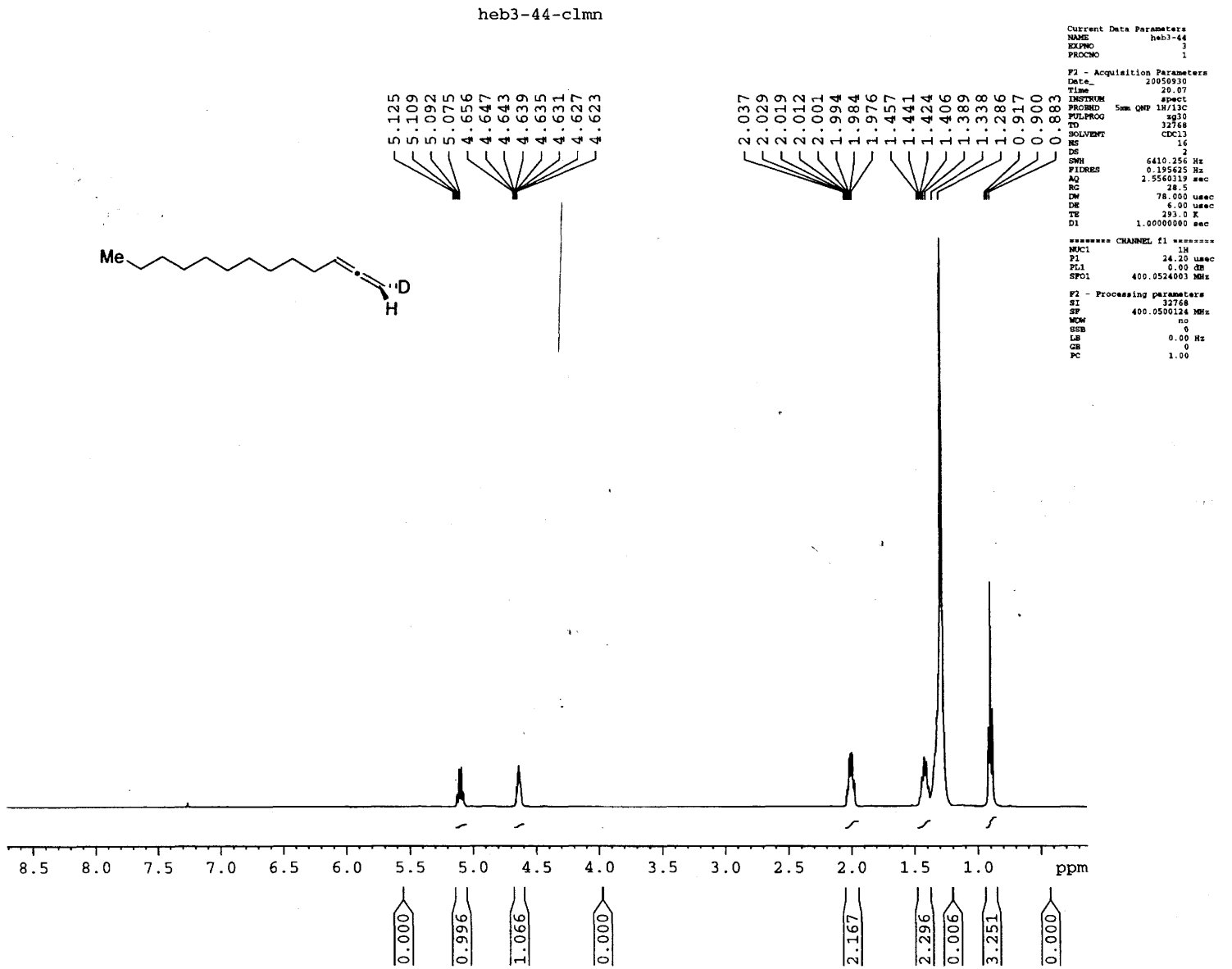
(*R*)-1-Deuteriotridec-1,2-diene (*R*)-2.23-d_1.[32] To a 2-neck 100-mL round-bottom flask with a magnetic stir bar, was added triphenylphosphine (1.01 g, 3.86 mmol) in THF (12 mL). This was cooled to -40 °C (ethylene glycol:ethanol, dry ice) and diethyl azodicarboxylate (607 μL, 3.86 mmol) was added slowly. The reaction stirred for 15 min at -40 °C when the labeled alkyne (586 mg, 2.66 mmol) was transferred by cannula as a solution in THF (9.1 mL). After an additional 15 min at -40 °C, *o*-nitrobenzenesulfonylhydrazine (NBSH, 838 mg, 3.86 mmol) was added as a solution in THF (12 mL). The reaction was stirred at -40 °C for an additional 2 h, then it was allowed to gradually warm to ambient temperature and allowed to stir overnight. The unpurified reaction mixture was concentrated, dissolved in methylene chloride and purified on silica gel (pentanes) to afford 263 mg (50% yield) of a clear oil.



(*R*)-2.23-d_1
>95% ee
90% D incorporation

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 6.8 Hz, C**H**$_3$CH$_2$), 1.29 (14H, s, br, (C**H**$_2$)$_7$), 1.38-1.45 (2H, m, C**H**$_2$CH$_2$CH), 2.00 (2H, qd, J = 7.2, 7.2, 7.1, 3.0 Hz, CH$_2$C**H**$_2$CH), 4.65-4.62 (1H, m, C**H**D), 5.09 (1H, q, J = 7.2, 6.8 Hz, CH$_2$C**H**C). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.9, 28.5, 29.3, 29.4, 29.5, 29.6, 28.9, 32.1, 74.4 (1C, t, $^1J_{CD}$ = 25.6 Hz), 90.3, 208.73. ^{2}H NMR (61.4 MHz, $CHCl_3$) δ 4.68. IR (neat) 2962 (s), 2924 (s), 2848(s), 1958 (s), 1458 (s), 1372 (m) cm^{-1}.

HRMS-CI GC/MS: for $C_{13}H_{23}D$ calc'd 181.194 (M^+), observed 181.193 (M^+). Purification: silica gel with pentanes afforded 263 mg (56% yield) of a clear oil. R_f = 0.92 (pentanes, developed with $KMnO_4$).


heb3-44-clmn
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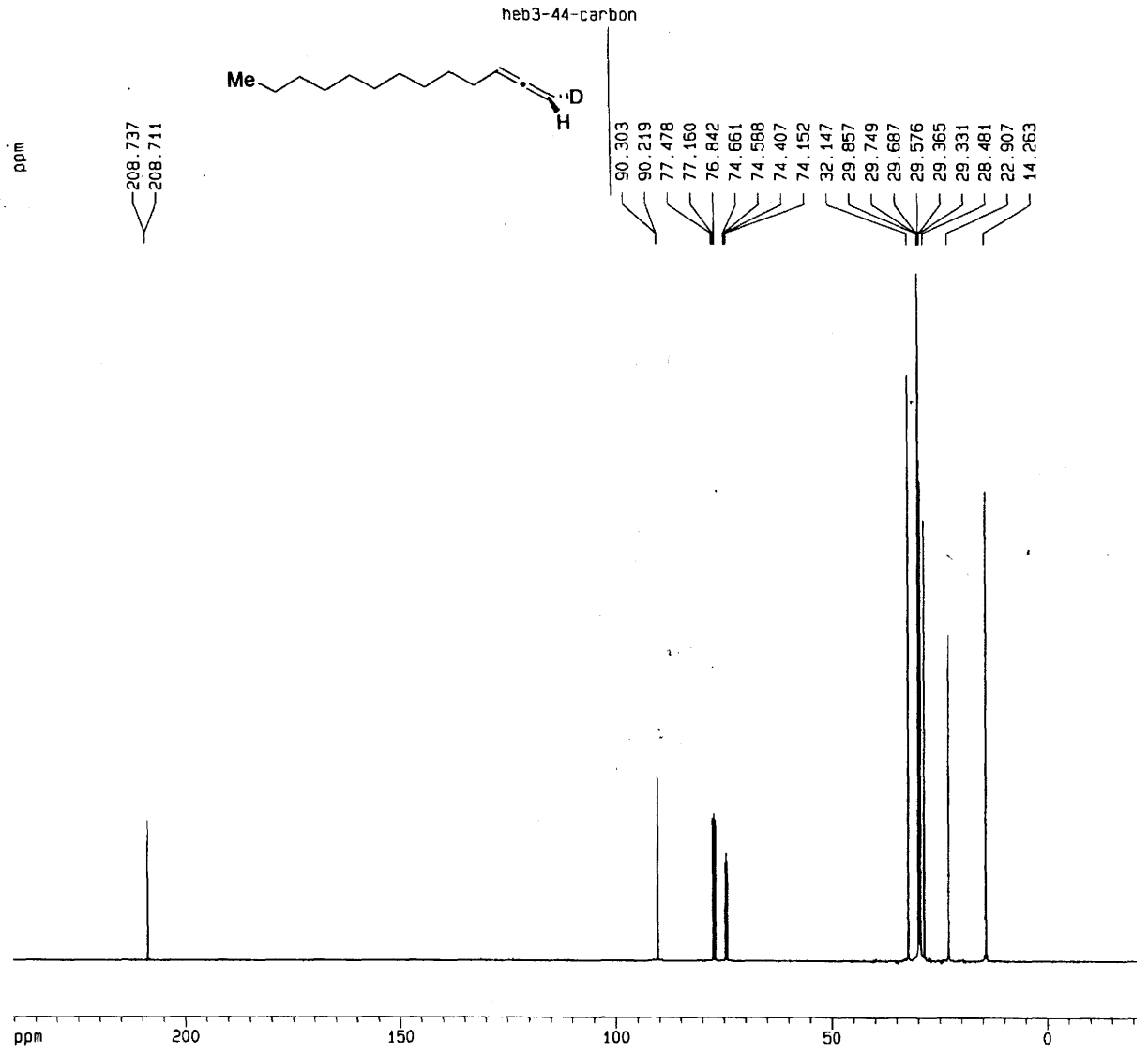
5.109
5.092
5.075
4.656
4.647
4.643
4.639
4.635
4.631
4.627
4.623
2.037
2.029
2.019
2.012
2.001
1.994
1.984
1.976
1.457
1.441
1.424
1.406
1.389
1.338
1.286
0.917
0.900
0.883
Me
D
H
Current Data Parameters
NAME heb3-44
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050930
Time 20.07
INSTRUM spect
PROBHD 5mm QNP 1H/13C
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6410.256 Hz
FIDRES 0.195625 Hz
AQ 2.5560319 sec
RG 28.5
DW 78.000 usec
DE 6.00 usec
TE 293.0 K
D1 1.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 24.20 usec
PL1 0.00 dB
SFO1 400.0524003 MHz
F2 - Processing parameters
SI 32768
SF 400.0500124 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.000
0.996
1.066
0.000
2.167
2.296
0.006
3.251
0.000

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Current Data Parameters
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EXPNO                       4
PROCNO                      1

F2 - Acquisition Parameters
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Time                   20.11
INSTRUM                spect
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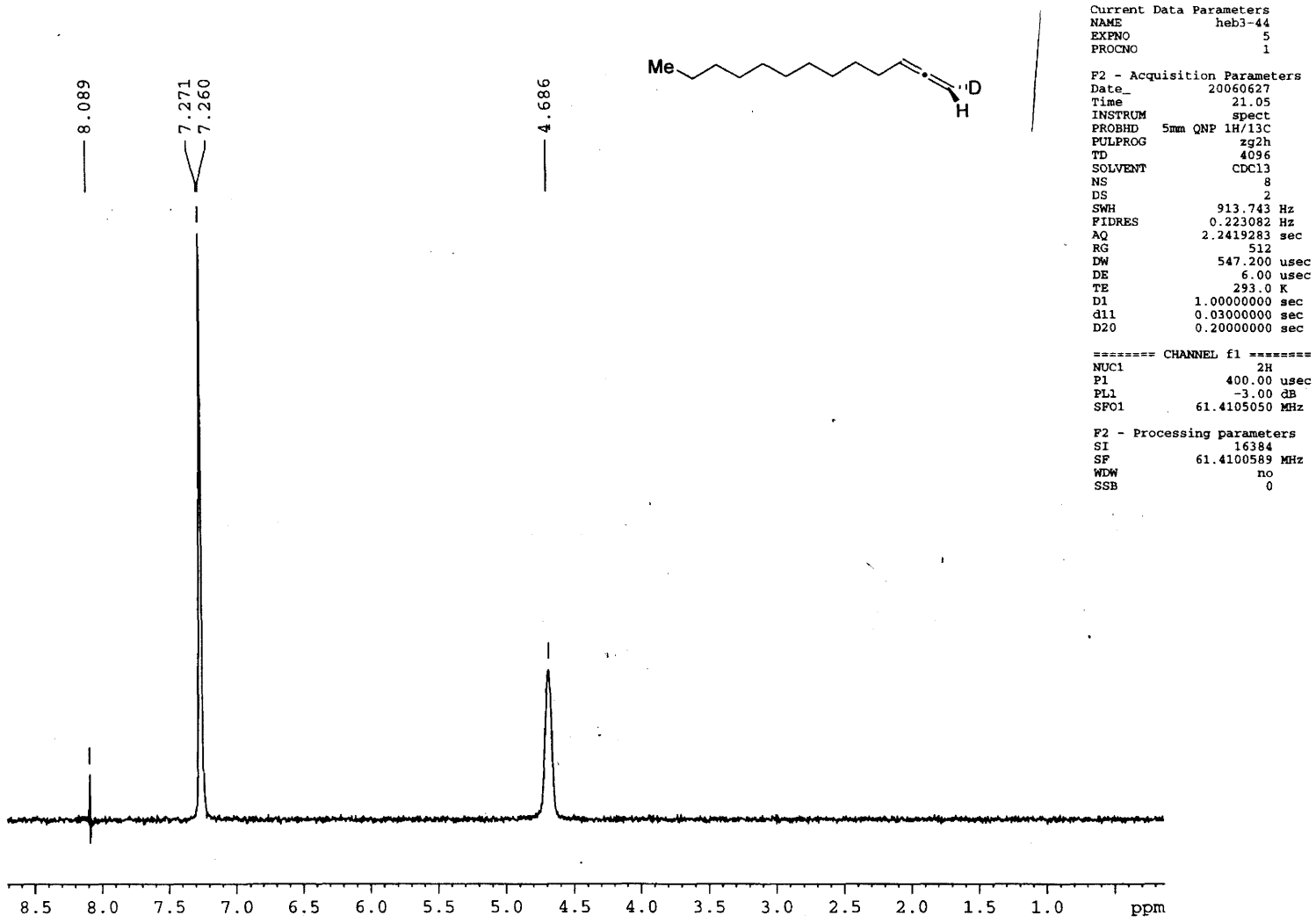
TD                      65536
SOLVENT                CDCl3
NS                      21019
DS                          2
SWH                26246.719 Hz
FIDRES                0.400493 Hz
AQ                    1.2485108 sec
RG                       6502
DW                      19.050 usec
DE                       6.00 usec
TE                      300.0 K
D1                    0.80000001 sec
d11                   0.03000000 sec
d12                   0.00002000 sec

======== CHANNEL f1 ========
NUC1                       13C
P1                        6.00 usec
PL1                       0.00 dB
SFO1               100.6036782 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                    80.00 usec
PL2                      -6.00 dB
PL12                     13.80 dB
PL13                     14.50 dB
SFO2               400.0516002 MHz

F2 - Processing parameters
SI                       32768
SF                 100.5926364 MHz
WDW                         no
SSB                          0
LB                        0.00 Hz
GB                           0
PC                        1.40

1D NMR plot parameters
CX                       20.00 cm
CY                       12.50 cm
F1P                     240.228 ppm
F1                     24165.13 Hz
F2P                    -20.693 ppm
F2                     -2081.59 Hz
PPMCM                 13.04604 ppm/cm
HZCM                1312.33594 Hz/cm
```



Current Data Parameters
NAME heb3-44
EXPNO 5
PROCNO 1

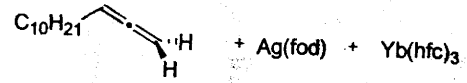
F2 - Acquisition Parameters
Date_ 20060627
Time 21.05
INSTRUM spect
PROBHD 5mm QNP 1H/13C
PULPROG zg2h
TD 4096
SOLVENT CDCl3
NS 8
DS 2
SWH 913.743 Hz
FIDRES 0.223082 Hz
AQ 2.2419283 sec
RG 512
DW 547.200 usec
DE 6.00 usec
TE 293.0 K
D1 1.00000000 sec
d11 0.03000000 sec
D20 0.20000000 sec

======== CHANNEL f1 ========
NUC1 2H
P1 400.00 usec
PL1 -3.00 dB
SFO1 61.4105050 MHz

F2 - Processing parameters
SI 16384
SF 61.4100589 MHz
WDW no
SSB 0

2.5.7.1. Enantiopurity determination of (R)-2.23-d_1.[33] To a 1-dram vial was added ytterbium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] ($Yb(hfc)_3$) (23.4 mg, 0.019 mmol) and (6,6,7,7,8,8-heptafluoro-2,2-dimethyl-3,5-octandionato)silver (Ag(fod)) (8.0 mg, 0.019 mmol). To this was added 750 μL of $CDCl_3$ and decyl allene (5.8 mg, 0.0321 mmol). ^1H NMR of the reference unlabeled decyl allene is below. The signals at δ 5.0 and 5.5 ppm correspond to the two terminal protons on the allene. A small amount of protonation was observed in ***(R)-2.23-d_1*** (δ 5.2 ppm).

heb2-129-ag/yb



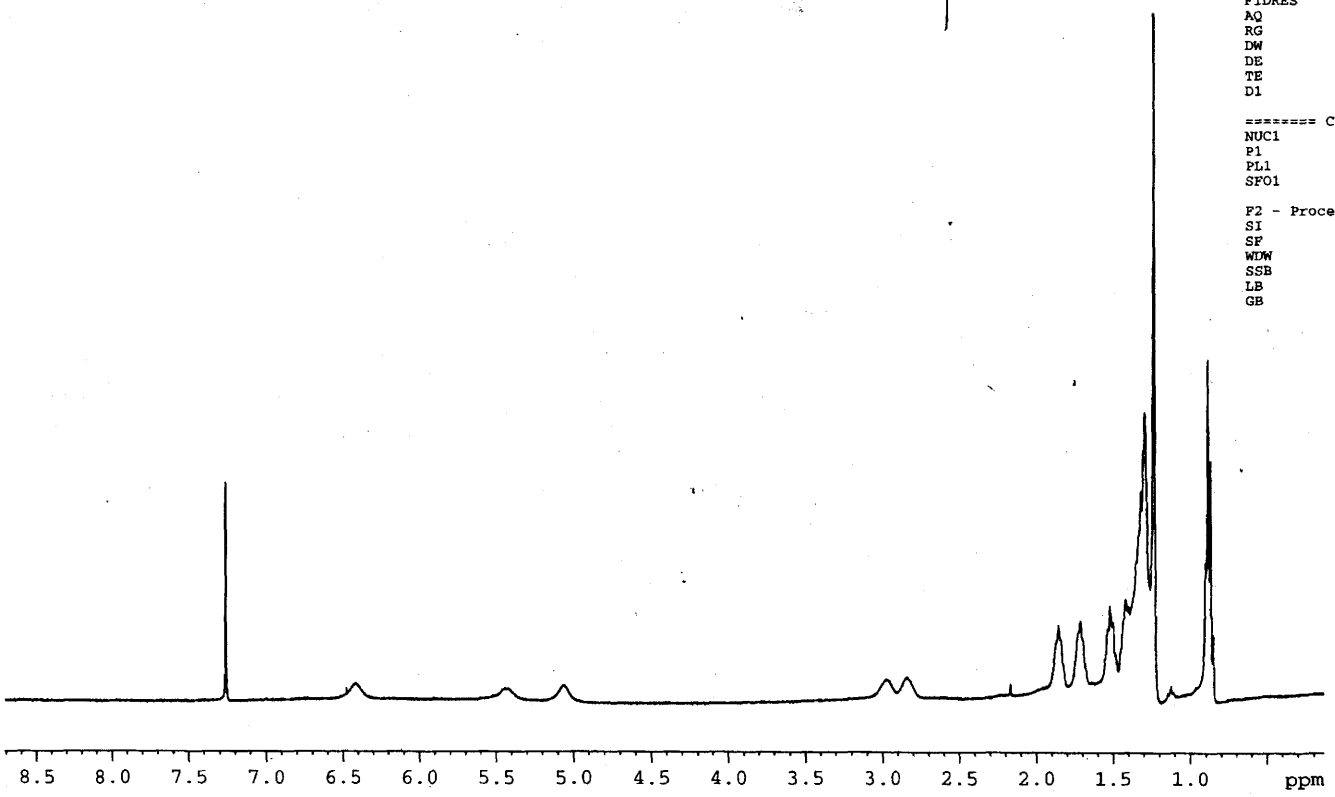
+ Ag(fod) + $Yb(hfc)_3$

```
Current Data Parameters
NAME                 heb2-129
EXPNO                       1
PROCNO                      1

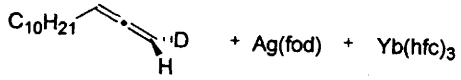
F2 - Acquisition Parameters
Date_               20050525
Time                   17.25
INSTRUM                spect
PROBHD    5mm QNP 1H/13C
PULPROG                zg30
TD                    32768
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                6410.256 Hz
FIDRES            0.195625 Hz
AQ                2.5560319 sec
RG                    228.1
DW                   78.000 usec
DE                    6.00 usec
TE                   293.0 K
D1                1.00000000 sec

======== CHANNEL f1 ========
NUC1                      1H
P1                     22.50 usec
PL1                     0.00 dB
SFO1           400.1326008 MHz

F2 - Processing parameters
SI                    32768
SF             400.1300095 MHz
WDW                      no
SSB                       0
LB                     0.00 Hz
GB                        0
```



heb3-52-



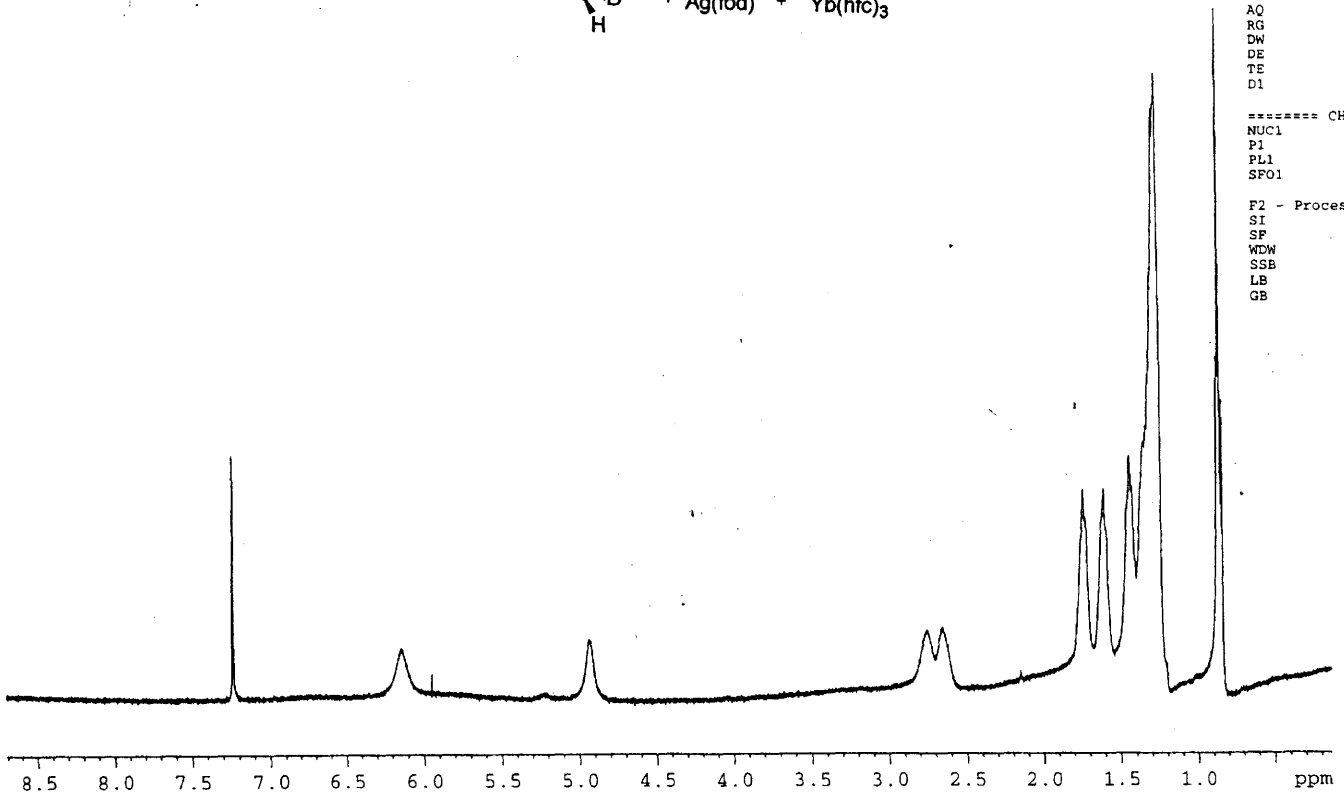
+ Ag(fod) + $Yb(hfc)_3$

```
Current Data Parameters
NAME                  heb3-52
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_              20051002
Time                  12.48
INSTRUM               spect
PROBHD    5mm QNP 1H/13C
PULPROG                zg30
TD                    32768
SOLVENT               CDCl3
NS                       15
DS                        2
SWH                6410.256 Hz
FIDRES            0.195625 Hz
AQ                2.5560319 sec
RG                    203.2
DW                   78.000 usec
DE                    6.00 usec
TE                   293.0 K
D1               1.00000000 sec

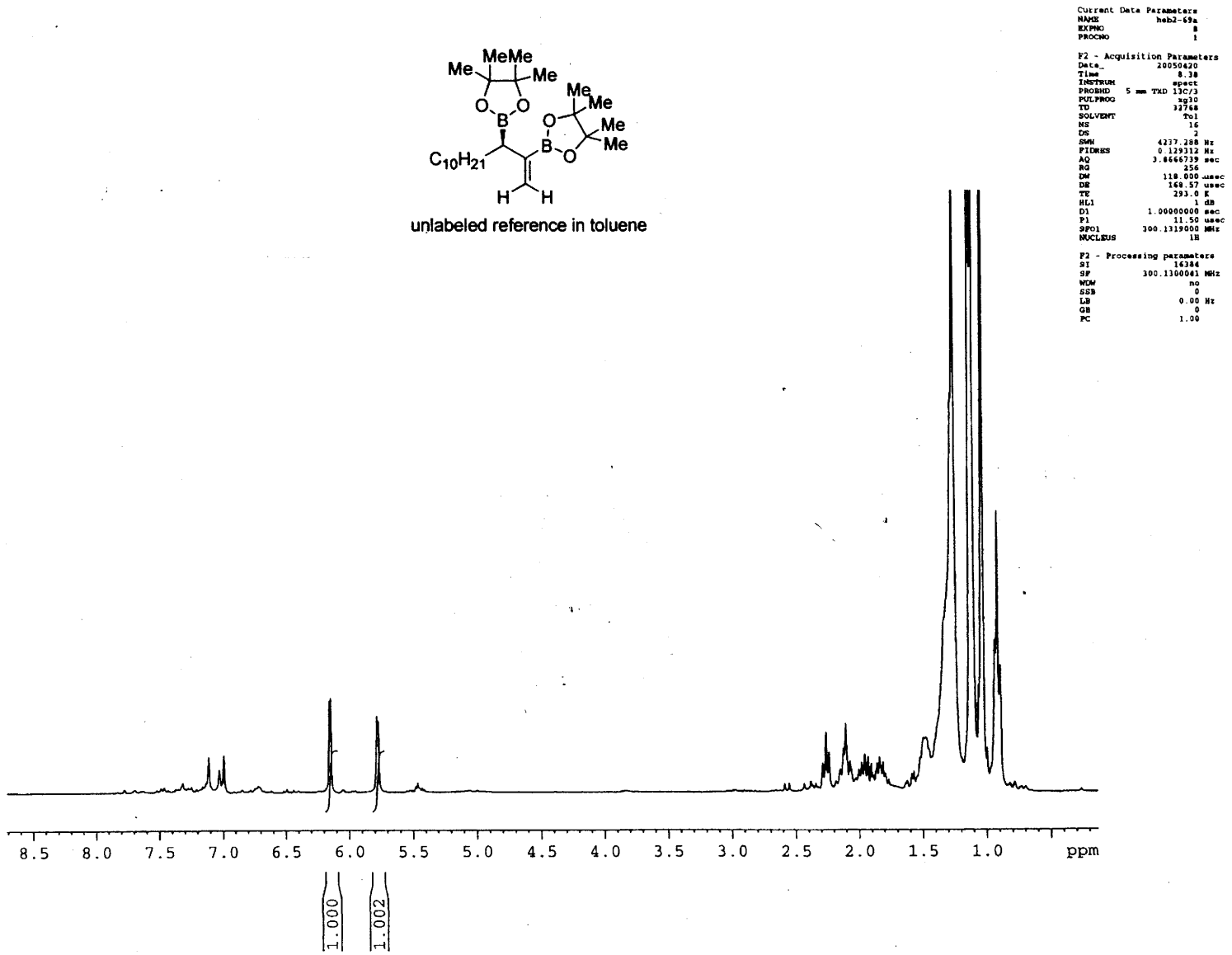
======== CHANNEL f1 ========
NUC1                    1H
P1                   24.20 usec
PL1                   0.00 dB
SFO1           400.0524003 MHz

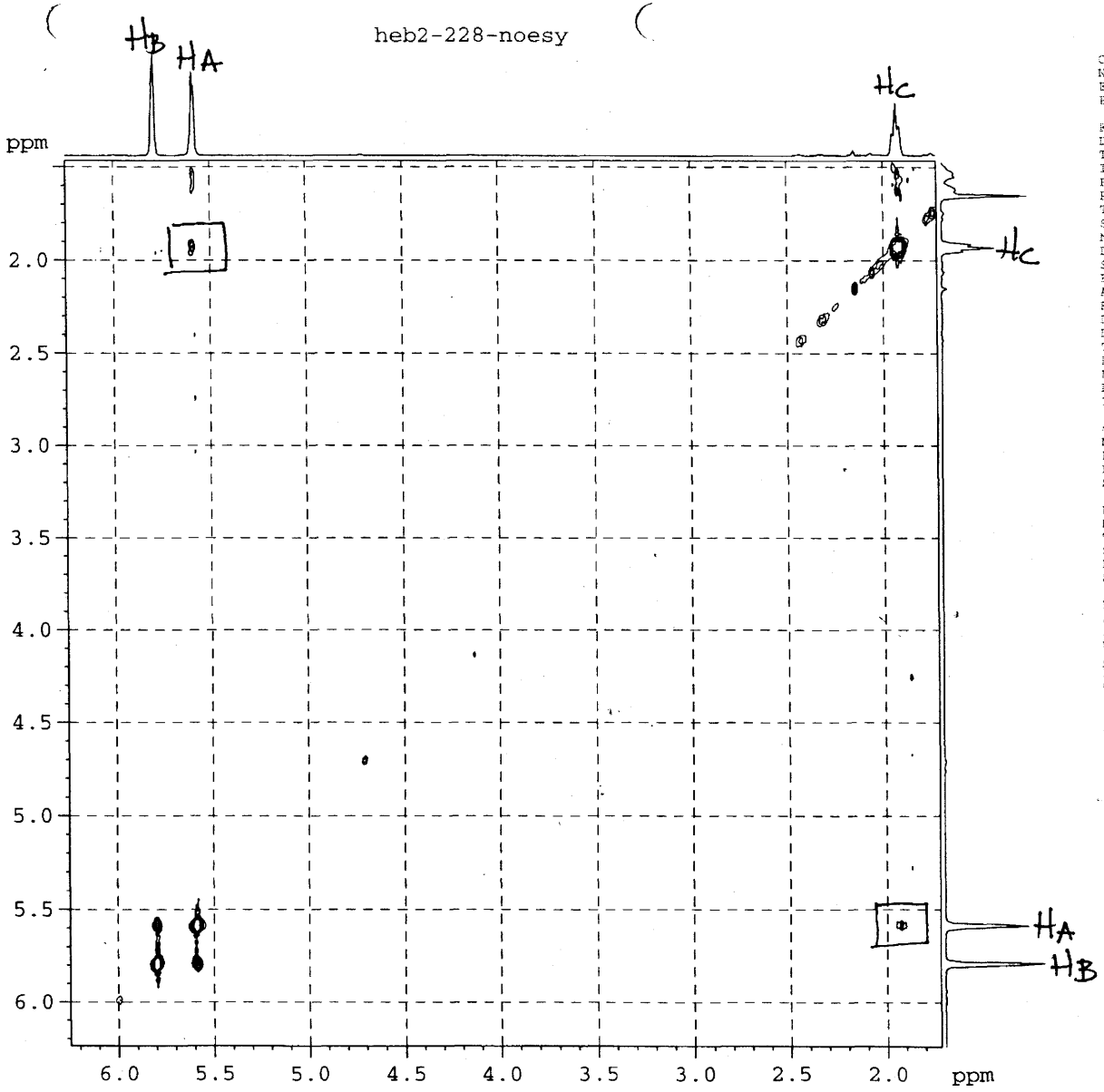
F2 - Processing parameters
SI                    32768
SF           400.0500200 MHz
WDW                      no
SSB                       0
LB                    0.00 Hz
GB                        0
```



2.5.8. Diboration of (*R*)-2.23-d_1.

In the dry box, a 1-dram vial equipped with a magnetic stir bar was charged with $Pd_2(dba)_3$ (4.0 mg, 0.0043 mmol) and (*R,R*)-xylylTADDOLPNMe$_2$ **(*R,R*)-2.17** (6.6 mg, 0.010 mmol). To this was added 300 μL of toluene-d_8. The metal/ligand mixture stirred for 1 h at which time $B_2(pin)_2$ (46.3 mg, 0.1824 mmol) was added followed by **(*R*)-2.23-d_1** (27.5 mg, 0.152 mmol). The reaction mixture was transferred to an oven-dried J-Young tube and diluted with the remaining 700 μL of toluene-d_8. The reaction was monitored by ^{1}H NMR every 17 min. After completion of the reaction, solvent was removed *in vacuo* and the unpurified material was purified on silica gel (2% ethyl acetate/hexanes) to afford 45.5 mg (68% yield) of the labeled product.


Me
Me
Me
Me
Me
Me
Me
O
O
B
O
B
O
$C_{10}H_{21}$
H
H
unlabeled reference in toluene
Current Data Parameters
NAME heb2-69a
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050420
Time 8.38
INSTRUM spect
PROBHD 5 mm TXD 13C/3
PULPROG zg30
TD 32768
SOLVENT Tol
NS 16
DS 2
SWH 4237.288 Hz
FIDRES 0.129312 Hz
AQ 3.8666739 sec
RG 256
DW 118.000 usec
DE 168.57 usec
TE 293.0 K
HL1 1 dB
D1 1.00000000 sec
P1 11.50 usec
SFO1 300.1319000 MHz
NUCLEUS 1H
F2 - Processing parameters
SI 16384
SF 300.1300041 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.000
1.002




```
Current Data Parameters
NAME                 heb2-228
EXPNO                       3
PROCNO                      1

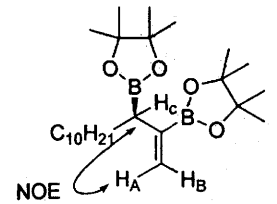
F2 - Acquisition Parameters
Date_               20050720
Time                   18.09
INSTRUM                spect
PROBHD     5mm QNP 1H/13C
PULPROG              noesytp
TD                      2048
SOLVENT                 CDCl3
NS                         8
DS                        16
SWH                 4084.967 Hz
FIDRES              1.994613 Hz
AQ                  0.2507252 sec
RG                       80.6
DW                   122.400 usec
DE                     6.00 usec
TE                    300.0 K
D0                  0.00000300 sec
D1                  1.50000000 sec
D8                  0.80000001 sec
IN0                 0.00012240 sec

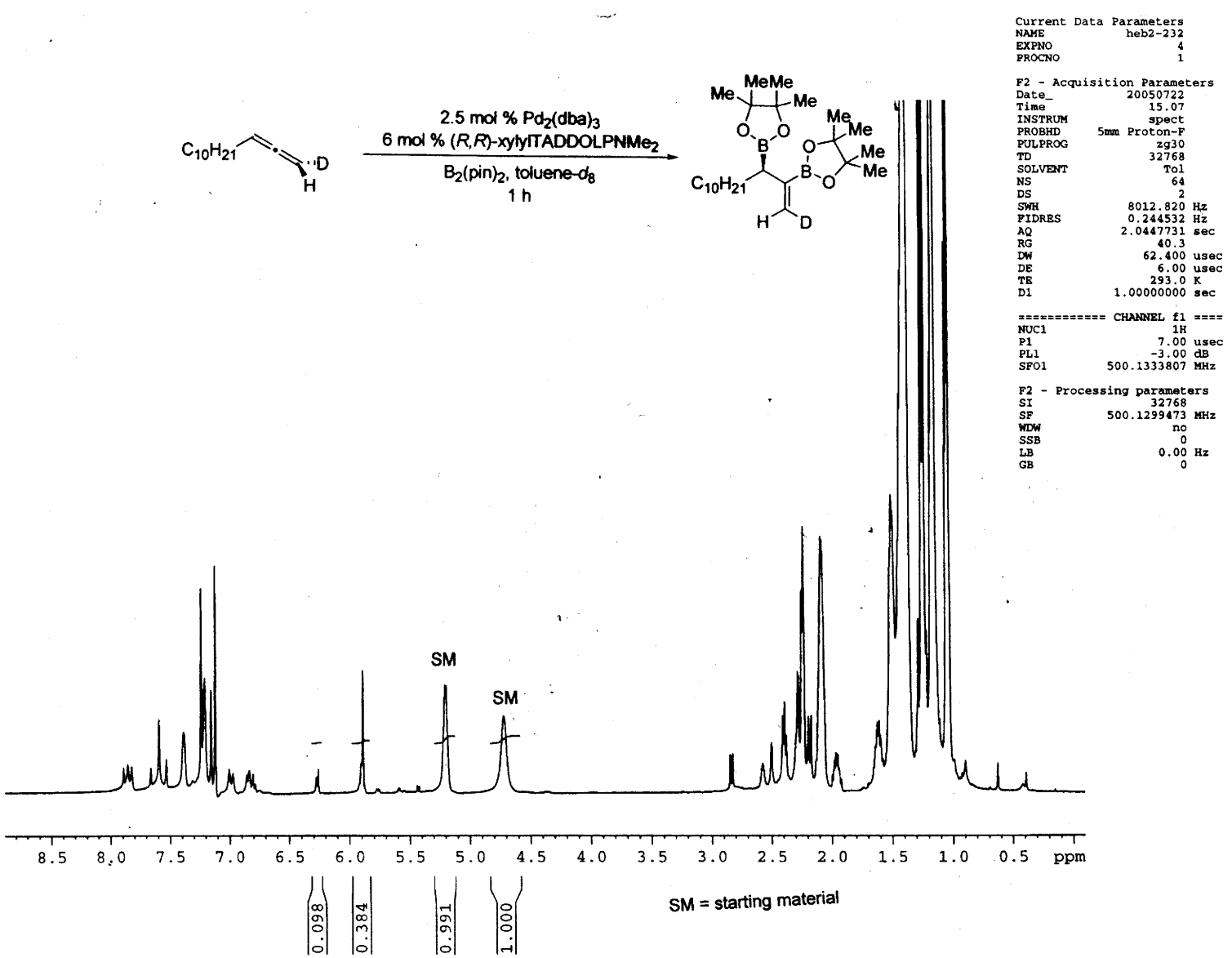
======== CHANNEL f1 ========
NUC1                      1H
P1                     13.40 usec
PL1                     0.00 dB
SFO1             400.1318419 MHz

F1 - Acquisition parameters
ND0                         2
TD                        512
SFO1                400.1318 MHz
FIDRES              7.976452 Hz
SW                     10.289 ppm

F2 - Processing parameters
SI                       1024
SF               400.1300000 MHz
WDW                     QSINE
SSB                         2
LB                       0.00 Hz
GB                          0
PC                       1.00

F1 - Processing parameters
SI                       1024
MC2                      TPPI
SF               400.1300000 MHz
```



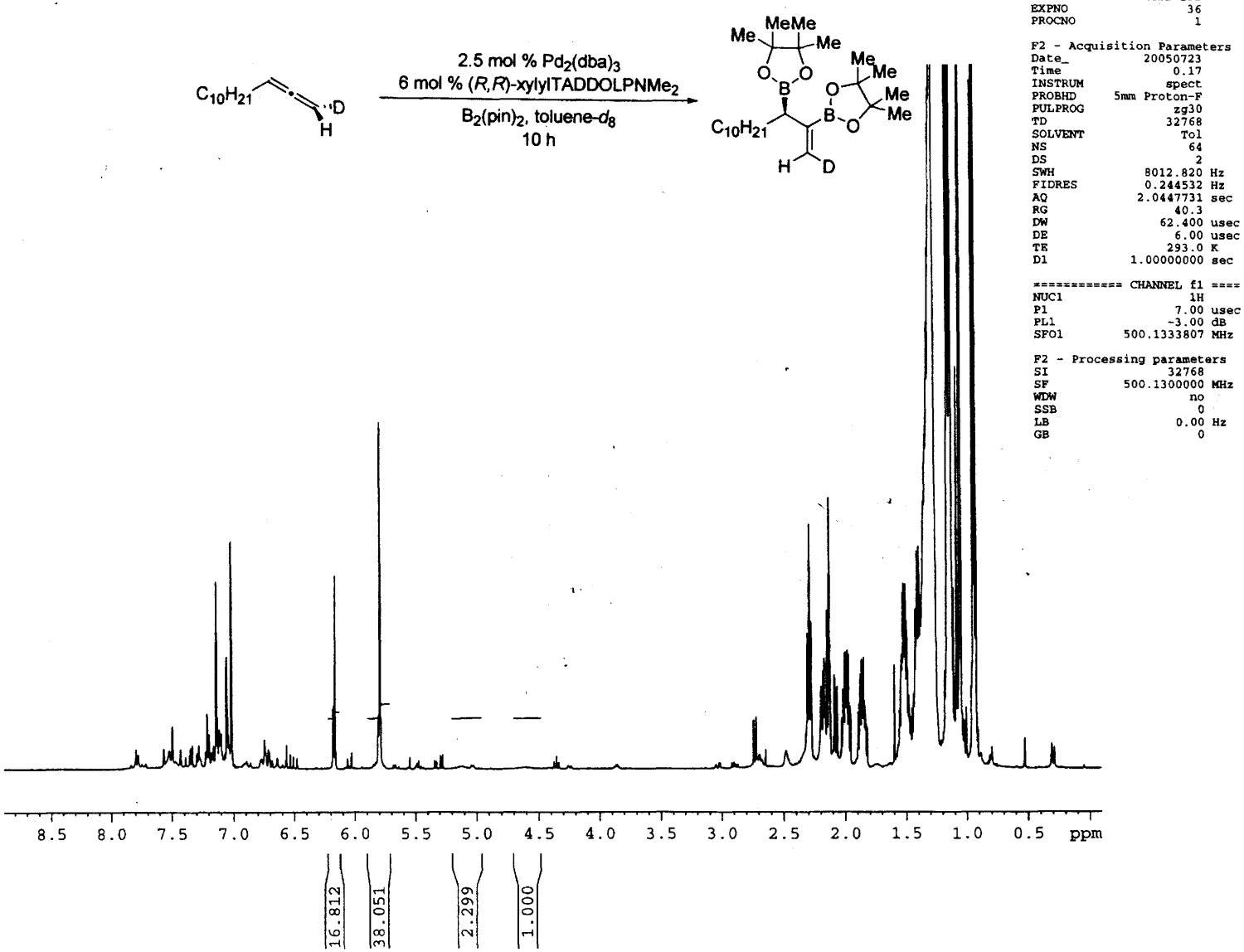


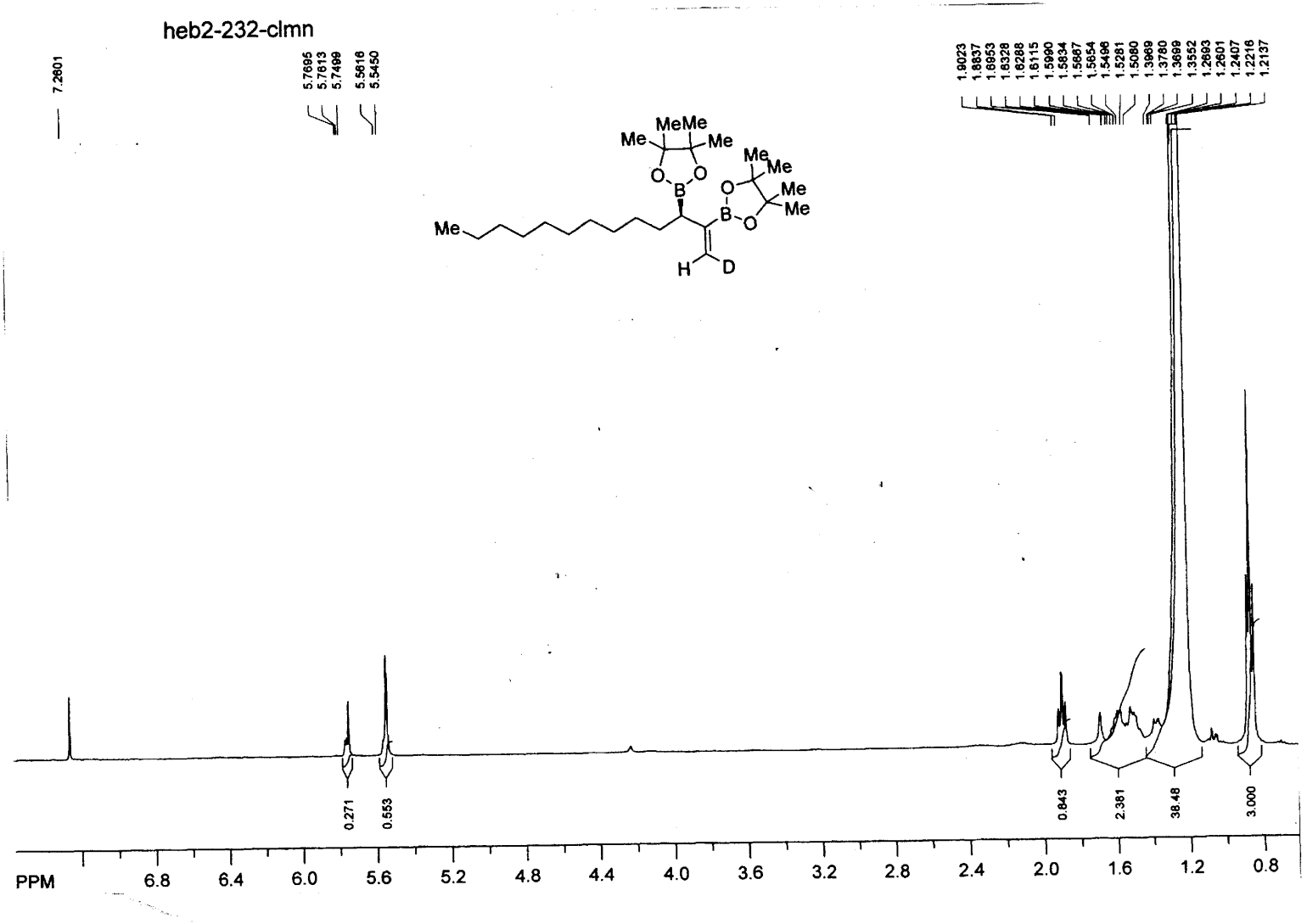

```
Current Data Parameters
NAME                  heb2-232
EXPNO                        4
PROCNO                       1

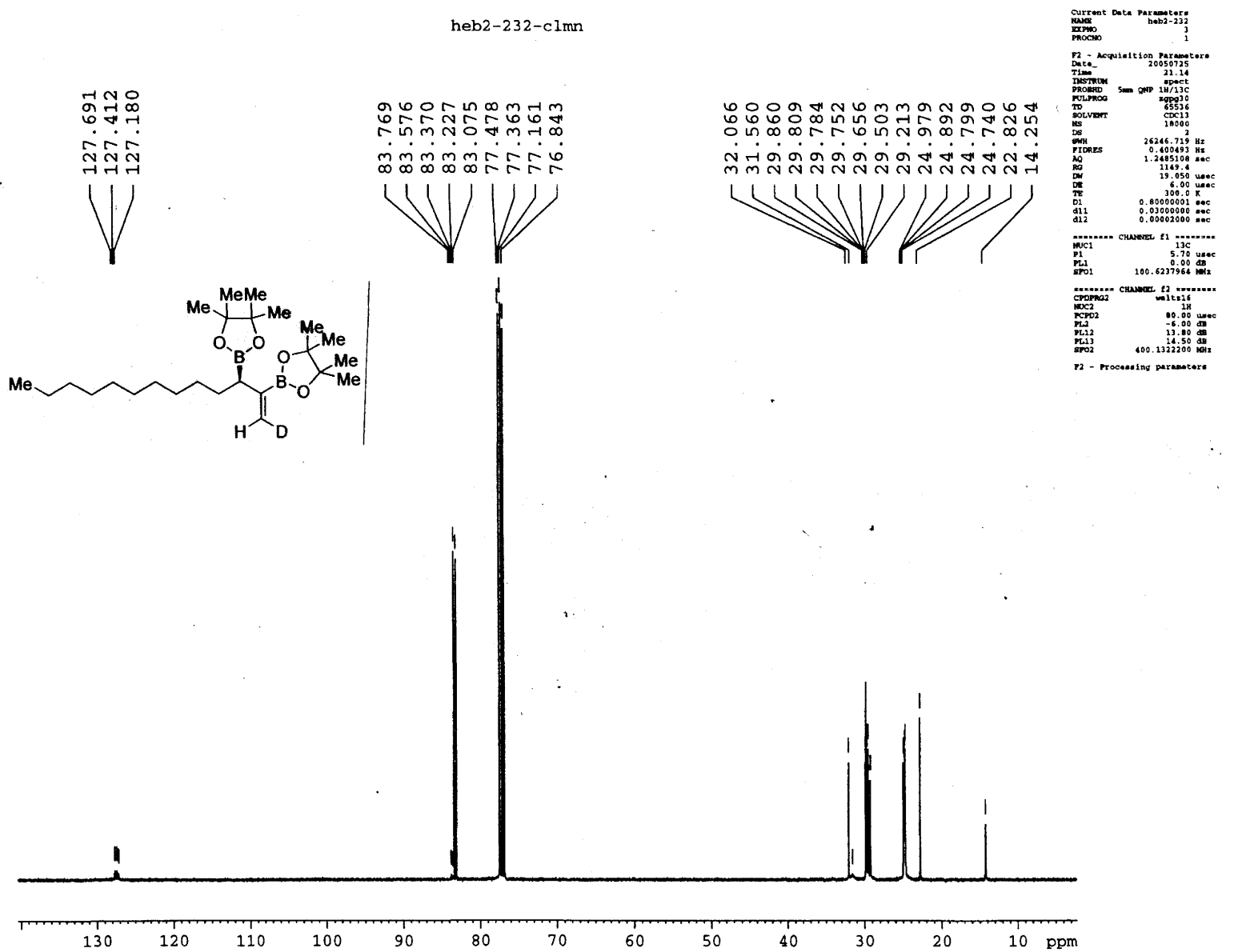
F2 - Acquisition Parameters
Date_                 20050722
Time                     15.07
INSTRUM                  spect
PROBHD       5mm Proton-F
PULPROG                  zg30
TD                      32768
SOLVENT                   Tol
NS                         64
DS                          2
SWH                8012.820 Hz
FIDRES             0.244532 Hz
AQ                 2.0447731 sec
RG                      40.3
DW                    62.400 usec
DE                     6.00 usec
TE                    293.0 K
D1                 1.00000000 sec

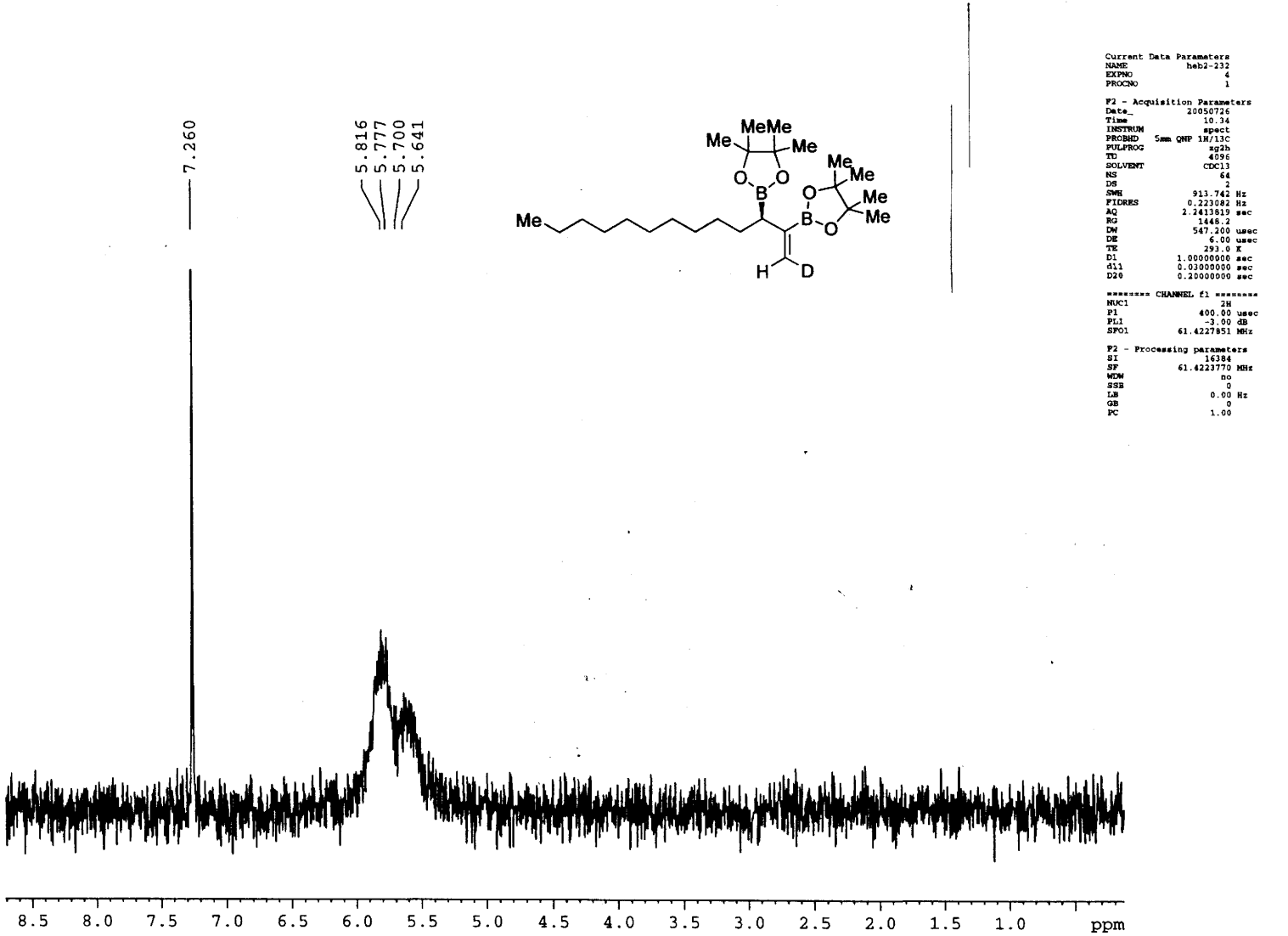
============ CHANNEL f1 ====
NUC1                       1H
P1                      7.00 usec
PL1                    -3.00 dB
SFO1              500.1333807 MHz

F2 - Processing parameters
SI                         32768
SF                500.1299473 MHz
WDW                           no
SSB                            0
LB                          0.00 Hz
GB                             0
```


2.5 mol % Pd2(dba)3
6 mol % (R,R)-xylylTADDOLPNMe2
B2(pin)2, toluene-d8
10 h
C10H21
D
H
Me
MeMe
Me
Me
Me
Me
O
B
O
B
O
O
C10H21
H
D
Current Data Parameters
NAME heb2-232
EXPNO 36
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050723
Time 0.17
INSTRUM spect
PROBHD 5mm Proton-F
PULPROG zg30
TD 32768
SOLVENT Tol
NS 64
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 2.04477731 sec
RG 40.3
DW 62.400 usec
DE 6.00 usec
TE 293.0 K
D1 1.00000000 sec
========== CHANNEL f1 ====
NUC1 1H
P1 7.00 usec
PL1 -3.00 dB
SFO1 500.1333807 MHz
F2 - Processing parameters
SI 32768
SF 500.1300000 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
16.812
38.051
2.299
1.000


heb2-232-clmn
7.2601
5.7695
5.7613
5.7499
5.5616
5.5450
1.9023
1.8837
1.8653
1.8328
1.8288
1.6115
1.5990
1.5834
1.5667
1.5654
1.5496
1.5281
1.5080
1.3969
1.3780
1.3699
1.3552
1.2693
1.2601
1.2407
1.2216
1.2137
Me
Me
Me
Me
Me
Me
Me
Me
B
B
O
O
O
O
H
D
0.271
0.553
0.843
2.381
38.48
3.000
PPM
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8


heb2-232-c1mn
127.691
127.412
127.180
83.769
83.576
83.370
83.227
83.075
77.478
77.363
77.161
76.843
32.066
31.560
29.860
29.809
29.784
29.752
29.656
29.503
29.213
24.979
24.892
24.799
24.740
22.826
14.254
Me
MeMe
Me
Me
Me
Me
Me
O
B
O
B
O
O
H
D
Current Data Parameters
NAME heb2-232
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050725
Time 21.14
INSTRUM spect
PROBHD 5mm QNP 1H/13C
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 18000
DS 2
SWH 26246.719 Hz
FIDRES 0.400493 Hz
AQ 1.2485108 sec
RG 1149.4
DW 19.050 usec
DE 6.00 usec
TE 300.0 K
D1 0.80000001 sec
d11 0.03000000 sec
d12 0.00002000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 5.70 usec
PL1 0.00 dB
SFO1 100.6237964 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -6.00 dB
PL12 13.80 dB
PL13 14.50 dB
SFO2 400.1322200 MHz
F2 - Processing parameters
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



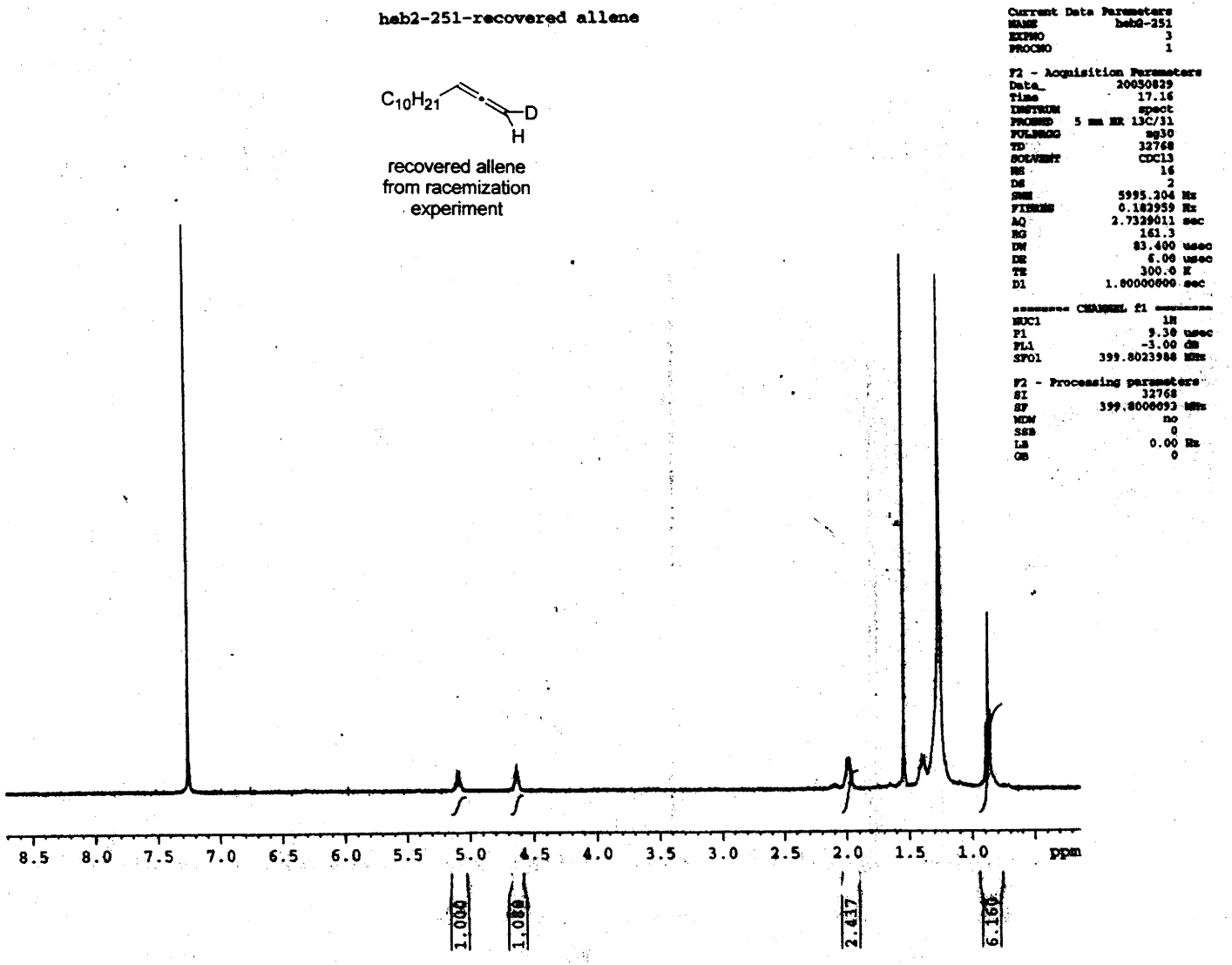
Current Data Parameters
NAME heb2-232
EXPNO 4
PROCNO 1

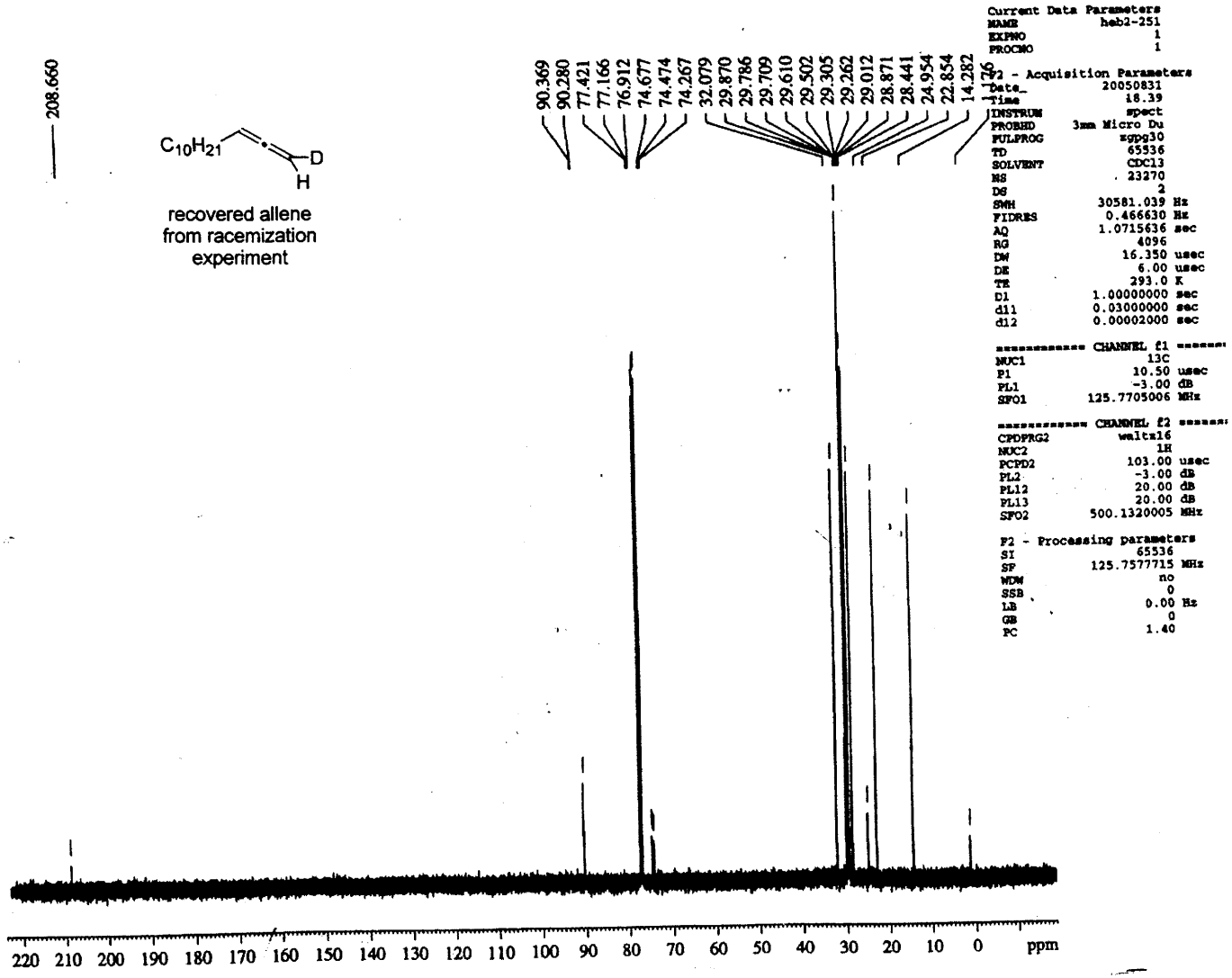
F2 - Acquisition Parameters
Date_ 20050726
Time 10.34
INSTRUM spect
PROBHD 5mm QNP 1H/13C
PULPROG zg2h
TD 4096
SOLVENT CDCl3
NS 64
DS 2
SWH 913.742 Hz
FIDRES 0.223082 Hz
AQ 2.2413819 sec
RG 1448.2
DW 547.200 usec
DE 6.00 usec
TE 293.0 K
D1 1.00000000 sec
d11 0.03000000 sec
D20 0.20000000 sec

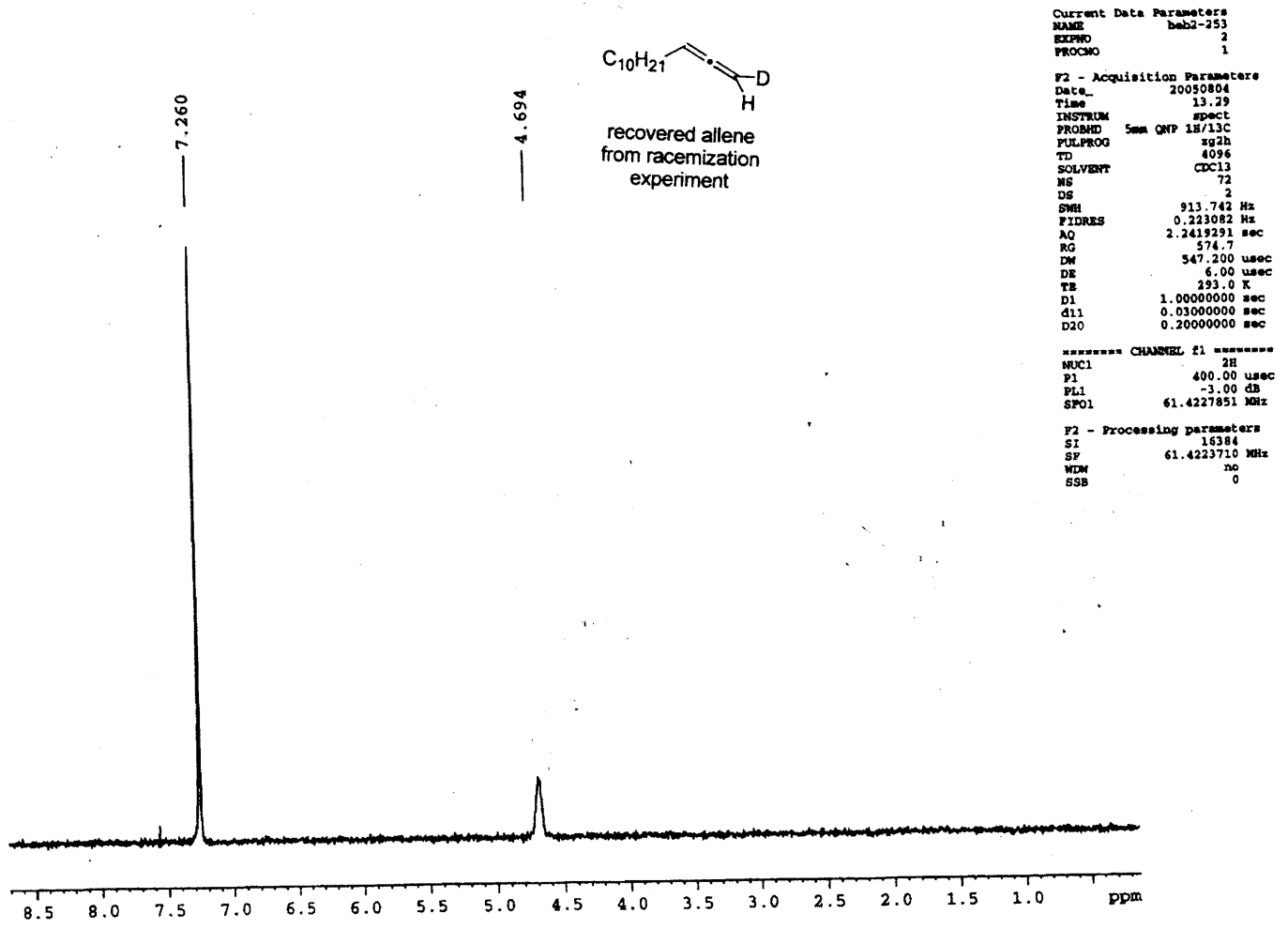
======== CHANNEL f1 ========
NUC1 2H
P1 400.00 usec
PL1 -3.00 dB
SFO1 61.4227851 MHz

F2 - Processing parameters
SI 16384
SF 61.4223770 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

2.5.9. Racemization Experiment with (*R*)-2.23-d_1. In the dry box, a 2-dram vial equipped with a stir bar was charged with $Pd_2(dba)_3$ (3.5 mg, 0.0038 mmol), (*R,R*)-xylylTADDOLPNMe$_2$ **(*R,R*)-2.17** (6 mg, 0.0091 mmol), and toluene (1 ml). The metal/ligand mixture complexed for 1 h at which time **(*R,R*)-2.23-d_1** (27.5 mg, 0.152 mmol) was added. The vial was sealed with a polypropylene cap and removed from the glove box. After 1 h, solvent was removed *in vacuo* and the unpurified reaction mixture was purified on silica gel (pentanes) to afford 7.4 mg (27%) of the recovered allene. Spectroscopic analysis with Yb(hfc)$_3$ and Ag(fod) indicated that the allene has racemized under the reaction conditions in the absence of $B_2(pin)_2$.


heb2-251-recovered allene
$C_{10}H_{21}$
D
H
recovered allene
from racemization
experiment
Current Data Parameters
NAME heb2-251
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050829
Time 17.16
INSTRUM spect
PROBHD 5 mm BB 13C/31
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 161.3
DW 83.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 9.30 usec
PL1 -3.00 dB
SFO1 399.8023988 MHz
F2 - Processing parameters
SI 32768
SF 399.8000093 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.000
1.088
2.437
6.160


208.660
90.369
90.280
77.421
77.166
76.912
74.677
74.474
74.267
32.079
29.870
29.786
29.709
29.610
29.502
29.305
29.262
29.012
28.871
28.441
24.954
22.854
14.282
$C_{10}H_{21}$
D
H
recovered allene
from racemization
experiment
Current Data Parameters
NAME heb2-251
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050831
Time 18.39
INSTRUM spect
PROBHD 3mm Micro Du
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 23270
DS 2
SWH 30581.039 Hz
FIDRES 0.466630 Hz
AQ 1.0715636 sec
RG 4096
DW 16.350 usec
DE 6.00 usec
TE 293.0 K
D1 1.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
CHANNEL f1
NUC1 13C
P1 10.50 usec
PL1 -3.00 dB
SFO1 125.7705006 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 103.00 usec
PL2 -3.00 dB
PL12 20.00 dB
PL13 20.00 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 65536
SF 125.7577715 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.40
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

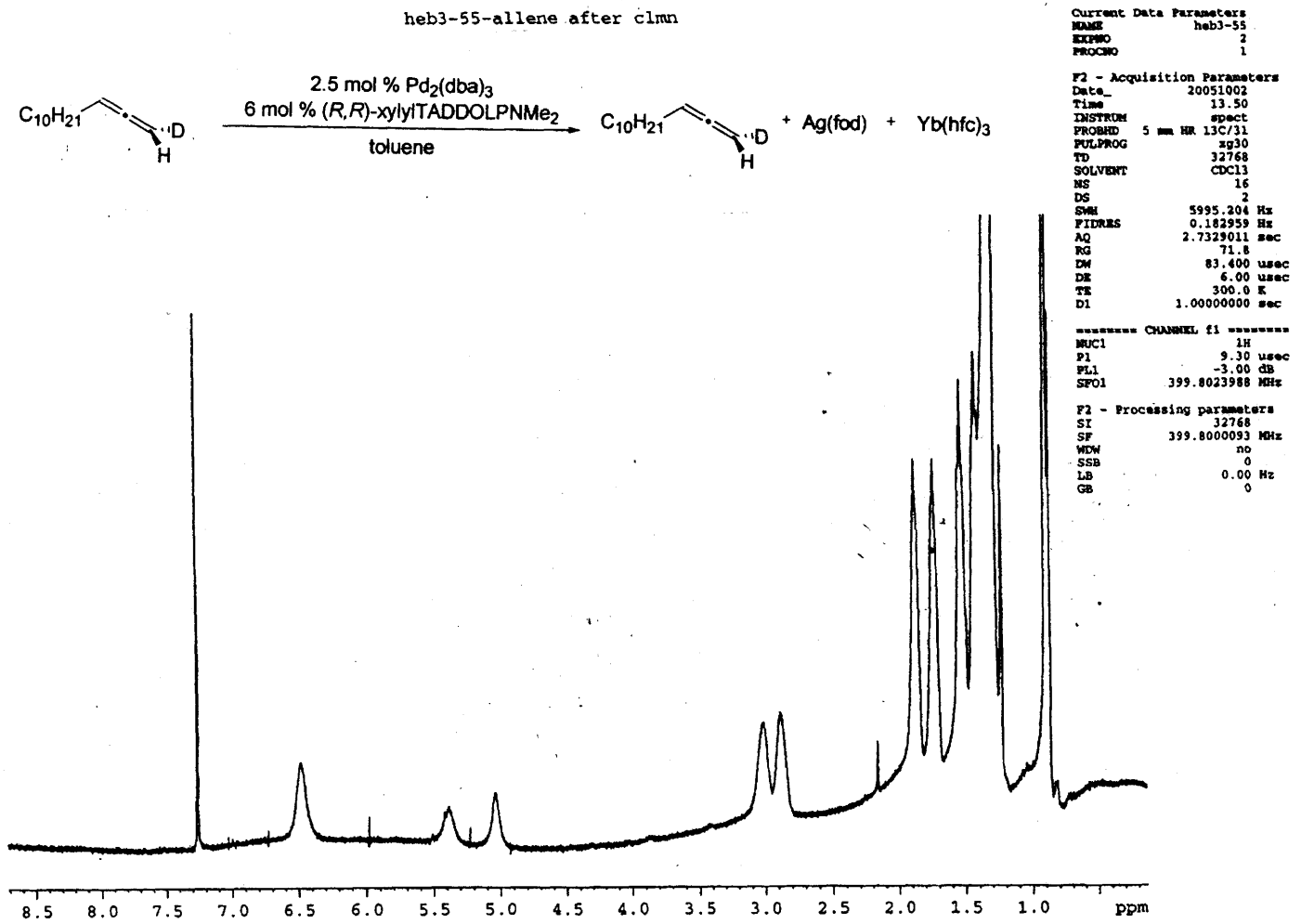



```
Current Data Parameters
NAME                  beb2-253
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_              20050804
Time                   13.29
INSTRUM                spect
PROBHD    5mm QNP 1H/13C
PULPROG                zg2h
TD                     4096
SOLVENT                CDCl3
NS                       72
DS                        2
SWH                913.742 Hz
FIDRES             0.223082 Hz
AQ                 2.2419291 sec
RG                     574.7
DW                 547.200 usec
DE                    6.00 usec
TE                    293.0 K
D1                 1.00000000 sec
d11                0.03000000 sec
D20                0.20000000 sec

======== CHANNEL f1 ========
NUC1                      2H
P1                   400.00 usec
PL1                   -3.00 dB
SFO1              61.4227851 MHz

F2 - Processing parameters
SI                       16384
SF                61.4223710 MHz
WDW                         no
SSB                          0
```


heb3-55-allene after clmn
$C_{10}H_{21}$
D
H
2.5 mol % $Pd_2(dba)_3$
6 mol % (R,R)-xylylTADDOLPNMe2
toluene
$C_{10}H_{21}$
D
H
+ Ag(fod) + $Yb(hfc)_3$
Current Data Parameters
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EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
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Time 13.50
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SOLVENT CDCl3
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DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
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PL1 -3.00 dB
SFO1 399.8023988 MHz
F2 - Processing parameters
SI 32768
SF 399.8000093 MHz
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SSB 0
LB 0.00 Hz
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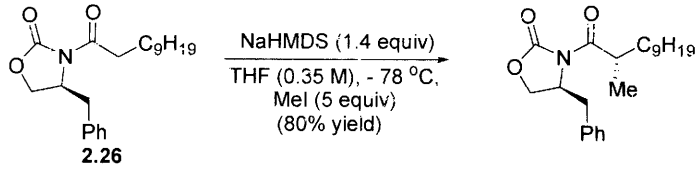
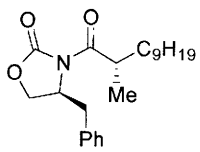
2.5.10. Synthesis of *(S)*-4-Methyl-trideca-1,2-diene 2.25.



2.26

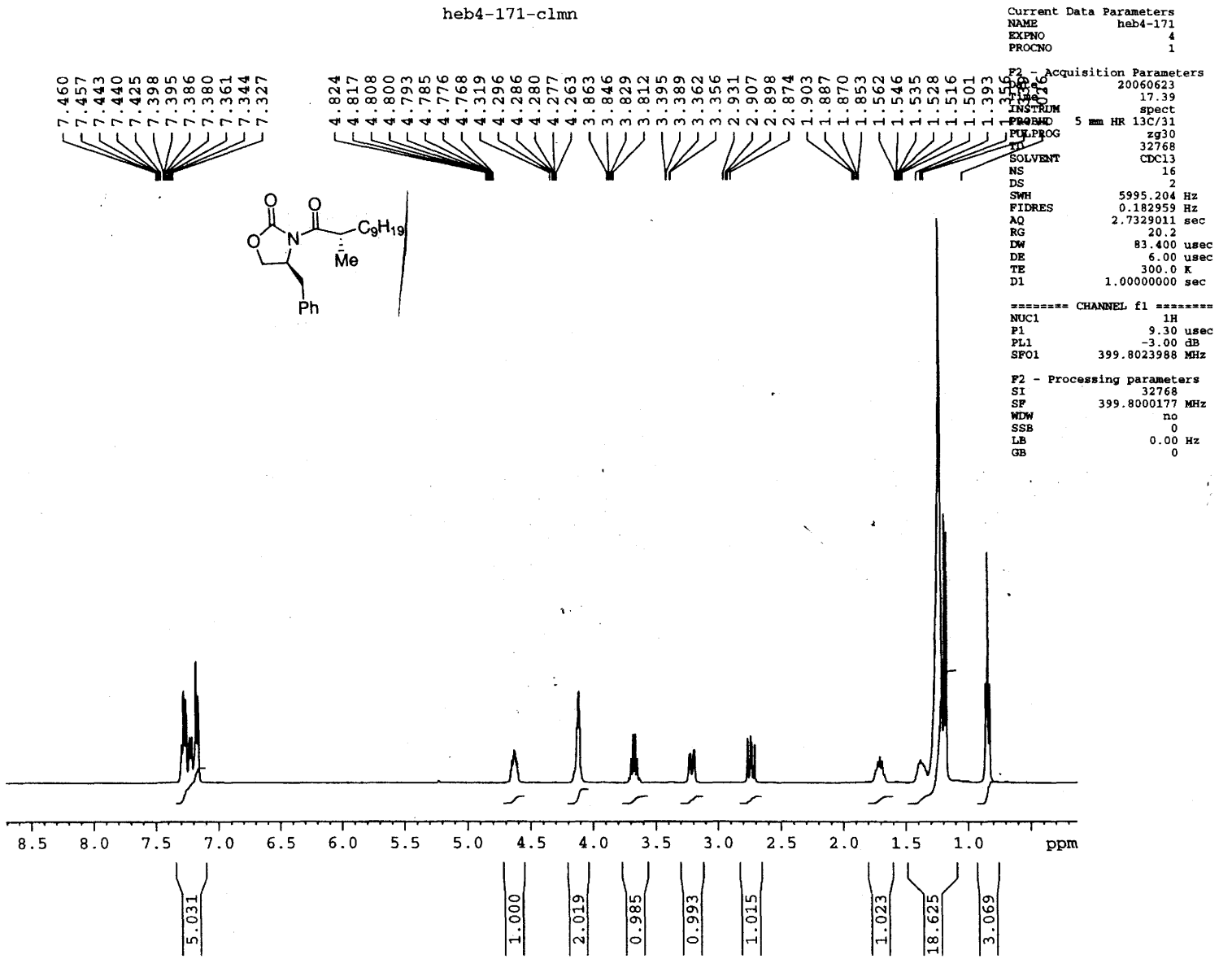
In the dry box, to a 50-mL pear-shaped flask was added NaHMDS (4.378 g, 25.23 mmol). The flask was removed from the dry box and NaHMDS was dissolved in THF (25 mL). To a separate 100-mL round-bottom flask with magnetic stir bar was added 4-benzyl-3-undecanoyl-oxazolidin-2-one **2.26** (6.200 g, 8.027 mmol), this was dissolved in THF (25 mL) and the flask was cooled to -78 °C (dry ice and isopropanol). The reaction stirred for 10 min before it was charged with the 1 M solution of NaHMDS. The reaction stirred at -78 °C for 1.5 h at which time methyl iodide (5.6 mL, 89.74 mmol) was added. The reaction continued to stir at -78 °C for 3 h when it was quenched with acetic acid (10 mL) and warmed to ambient temperature. The reaction was diluted with water and ethyl acetate, and the aqueous layer was extracted 3 times with ethyl acetate. The organic layers were combined, dried ($MgSO_4$), and filtered over Celite. The organic solution was concentrated and purified on silica gel (10% ethyl acetate/hexanes) to afford (*S*)-4-benzyl-3-((*S*)-2-methylundecanoyl)oxazolidin-2-one as a clear oil (5.117 g, 80% yield).



(*S*)-4-Benzyl-3-((*S*)-2-methylundecanoyl)oxazolidin-2-one. [50] ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (3H, t, J = 6.8 Hz, CH_2CH_3), 1.35 (3H, d, J = 6.8 Hz, CH_3CH), 1.39-1.56 (14H, m, $(CH_2)_7$), 1.50-1.56 (1H, m,

(50) Ghosh, A.K.; Gong, G. *J. Am. Chem. Soc.* **2004**, *126*, 3704-3705.

CHC$\mathbf{H_A}$H$_B$), 1.85-1.90 (1H, m, CHCH$_A$$\mathbf{H_B}$), 2.90 (1H, dd, J = 13.2, 9.6 Hz, C$\mathbf{H_A}$H$_B$Ph), 3.38 (1H, dd, J = 13.2, 2.4 Hz, CH$_A$$\mathbf{H_B}$Ph), 3.81-3.86 (1H, m, COC**H**), 4.26-4.31 (2H, m, OC$\mathbf{H_2}$CH), 4.76-4.79 (1H, m, CH$_2$C**H**N), 7.32-7.46 (5H, m, Ar-**H**). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 17.4, 22.6, 27.3, 29.3, 29.5, 29.6, 31.9, 33.4, 37.7, 37.8, 55.3, 65.9, 127.3, 128.8, 129.4, 135.4, 153.0, 177.3. IR (neat): 3538 (w), 3359 (w), 3028 (s), 2962 (s), 1779 (s), 1708 (s), 1458 (s) cm^{-1}. LRMS-(ESI+): for $C_{22}H_{33}NNaO_3$ calc'd 382.2 $(M+Na)^+$, observed: 382.3 $(M+Na)^+$. Purification: silica gel with 10% ethyl acetate/hexanes afforded 5 117 g (80% yield) of a clear oil. R_f = 0.53 (10% ethyl acetate/hexanes, UV active).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AQ 2.7329011 sec
RG 20.2
DW 83.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
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7.425
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7.361
7.344
7.327
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4.280
4.277
4.263
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2.898
2.874
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1.887
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1.546
1.535
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1.516
1.501
1.393
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3.0
2.5
2.0
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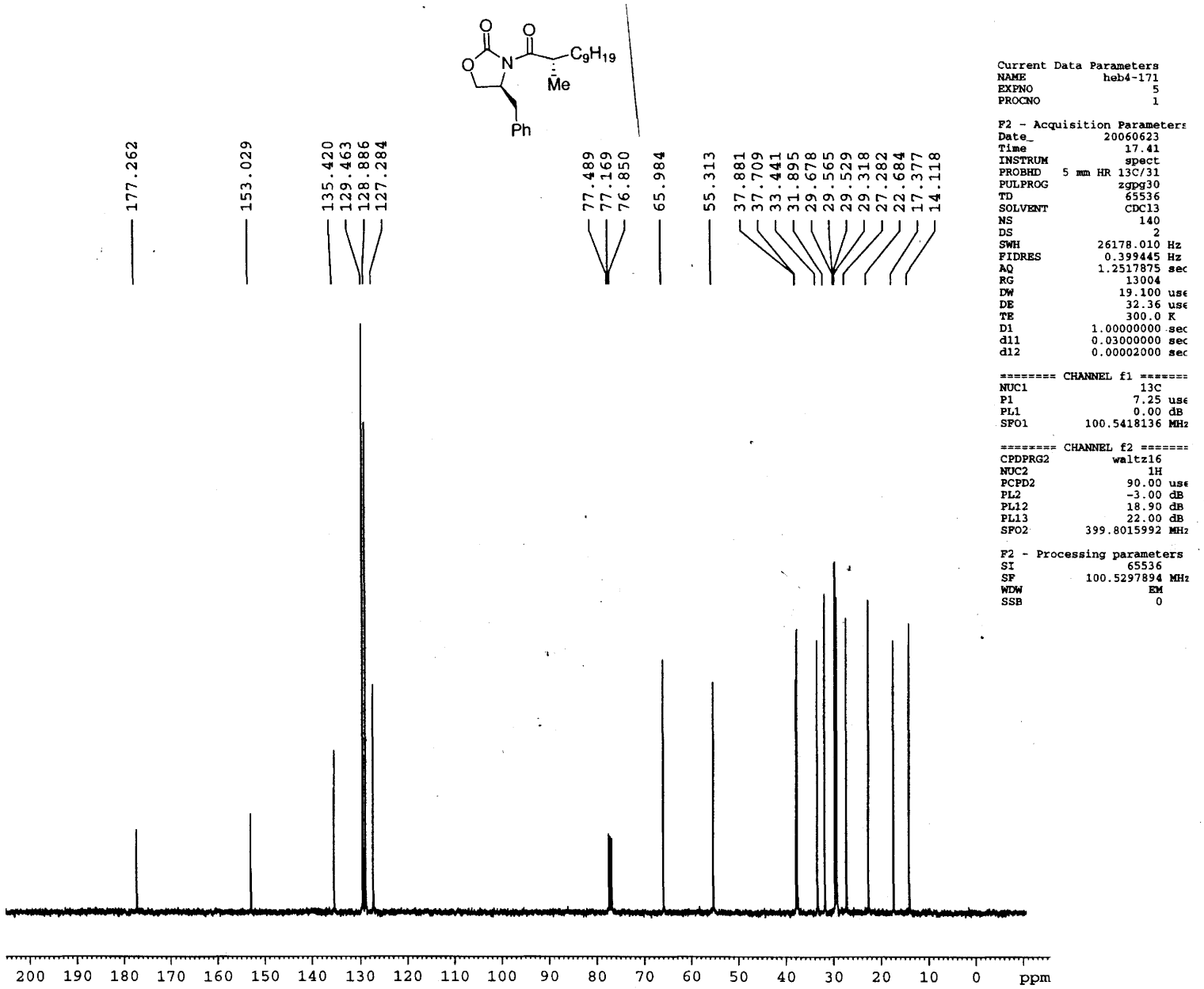

Current Data Parameters

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PROCNO	1

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======== CHANNEL f2 =======

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F2 - Processing parameters

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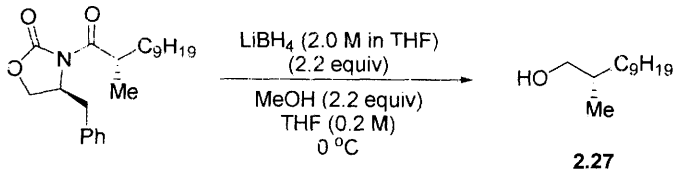
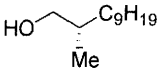


2.27

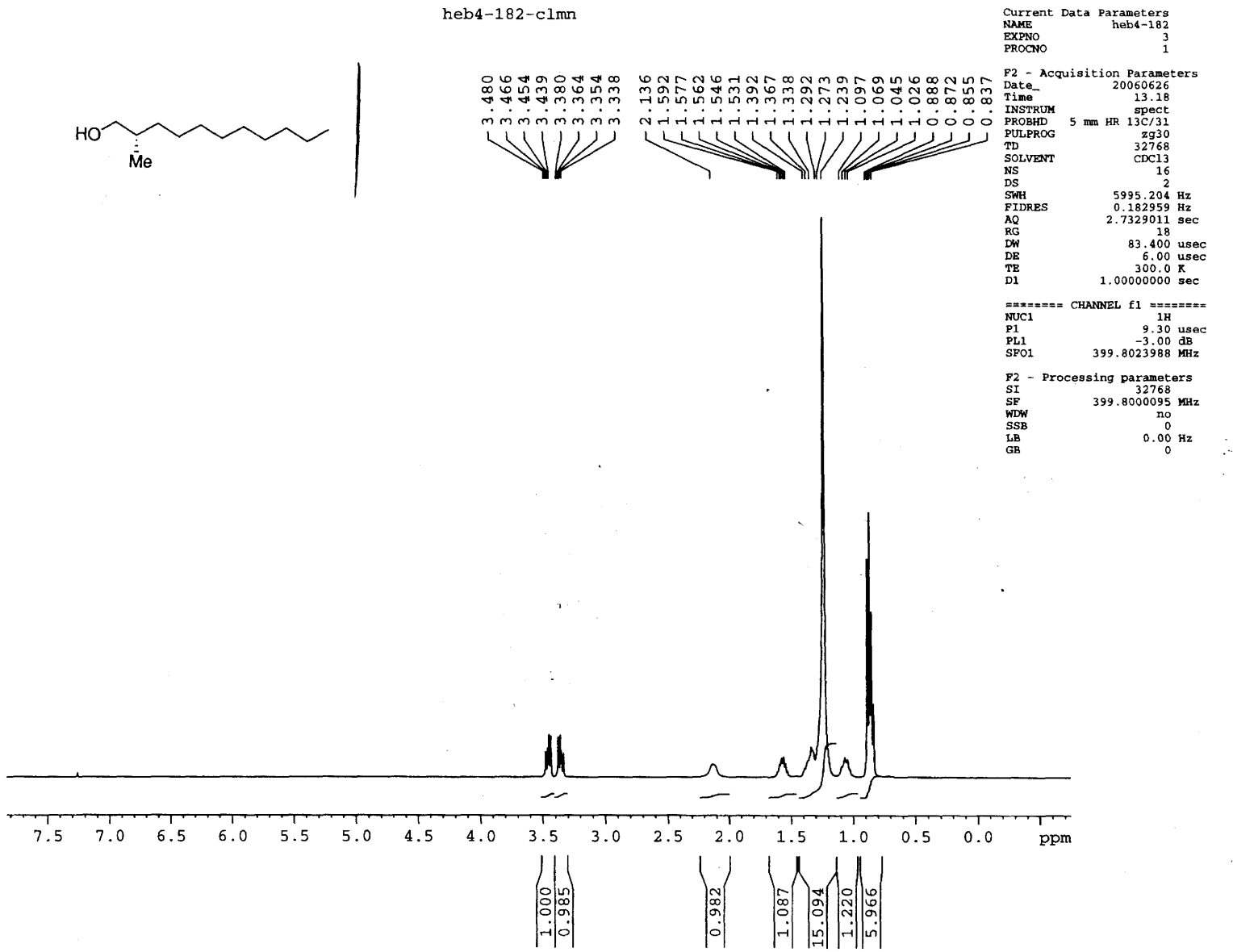
To a 250-mL round-bottom flask with magnetic stir bar was added (*S*)-4-benzyl-3-((*S*)-2-methylundecanoyl)oxazolidin-2-one (3.500 g, 9.819 mmol) in THF (49 mL, 0.2 M). Methanol (874 μL, 21.6 mmol) was added and the flask was cooled to 0 °C (ice-water bath). The reaction mixture stirred for 10 min at which time it was charged with $LiBH_4$ (2.0 M in THF, 10.8 mL). The reaction stirred for 3 h at 0 °C, when it was quenched with 10% NaOH and diluted with dichloromethane. The reaction was warmed to ambient temperature and the aqueous layer was washed three times with dichloromethane. The organic extracts were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated. The resulting oil was purified on silica gel (10% ethyl acetate/hexanes) to afford 269 mg (90% yield) of (*S*)-2-methyl-undecan-1-ol as a clear oil.



2.27

(*S*)-2-Methylundecan-1-ol (2.27). ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (3H, t, J = 6.8 Hz, CH_2CH_3), 0.87 (3H, d, J = 6.4 Hz, CH_3CH), 1.06 (1H, q, J = 9.3 Hz, $CHCH_AH_BCH_2$) 1.23-1.39 (14H, m, $(CH_2)_7$), 1.38-1.39 (1H, m, $CHCH_AH_BCH_2$), 1.56 (1H, m, $HCCH_3$), 2.14 (1H, br s, OH), 3.34 (1H, dd, J = 10.4, 6.4 Hz, $HOCH_AH_BCH$), 3.46 (1H, dd, J = 10.6, 6.0 Hz, $HOCH_AH_BCH$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 16.7, 22.8, 27.1, 29.5, 29.7, 29.8, 30.0, 32.0, 33.3, 35.9, 68.4. IR (neat): 3337 (br), 2924 (s), 2848 (s), 1458 (s) 1371 (m) cm^{-1}. LRMS-(ESI+): for $C_{12}H_{27}O$

calc'd: 187.2 $(M+H)^+$, observed: 187.1 $(M+H)^+$. Purification: silica gel with 10% ethyl acetate/hexanes afforded 269.2 mg (90% yield) of a clear oil. R_f = 0.22 (10% ethyl acetate/hexanes, stain in PMA).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1.546
1.531
1.392
1.367
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1.026
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FIDRES 0.182959 Hz
AQ 2.7329011 sec
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TE 300.0 K
D1 1.00000000 sec
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6.0
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3.0
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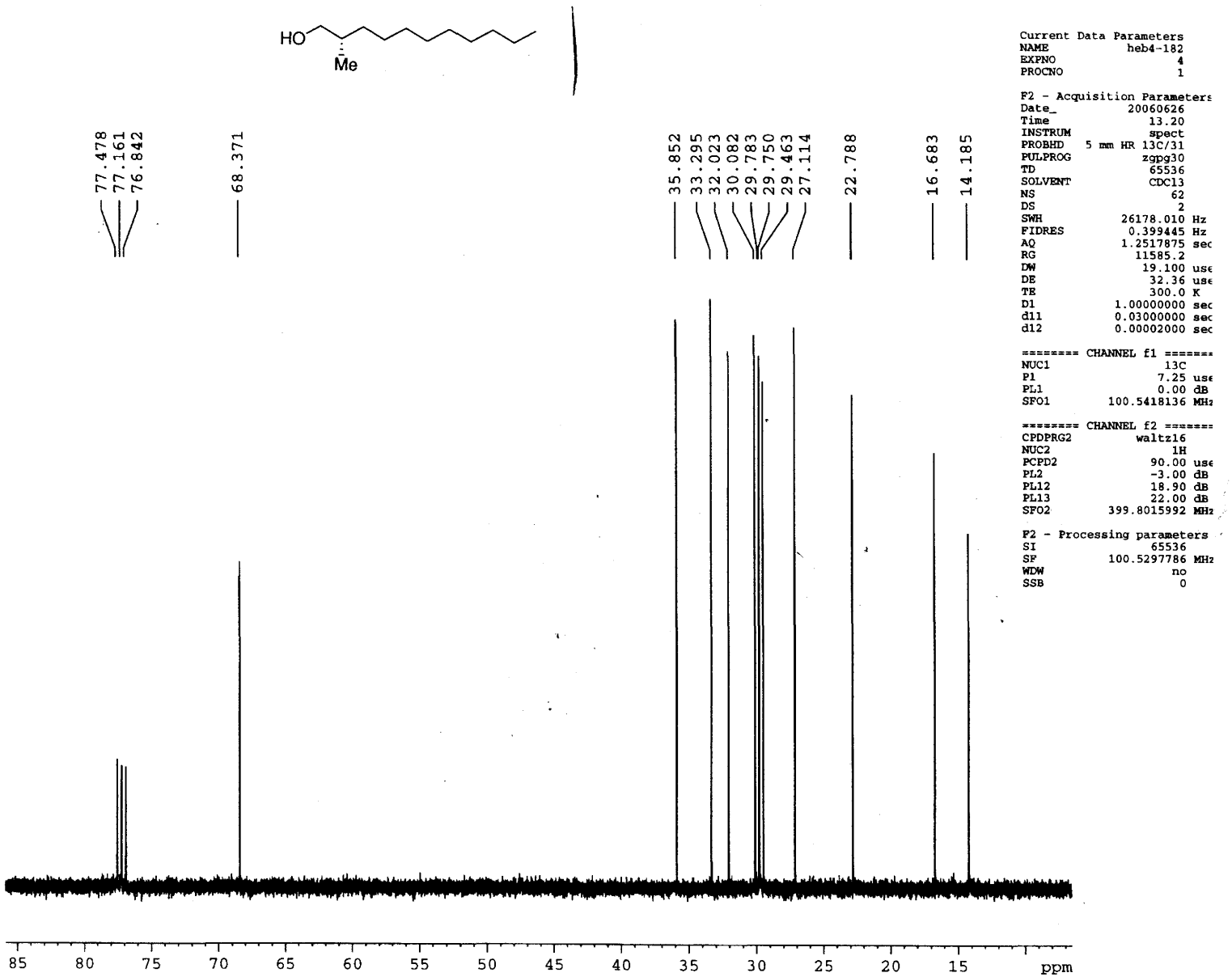
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20
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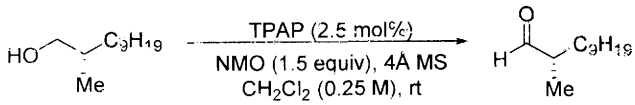
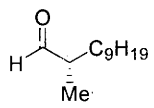
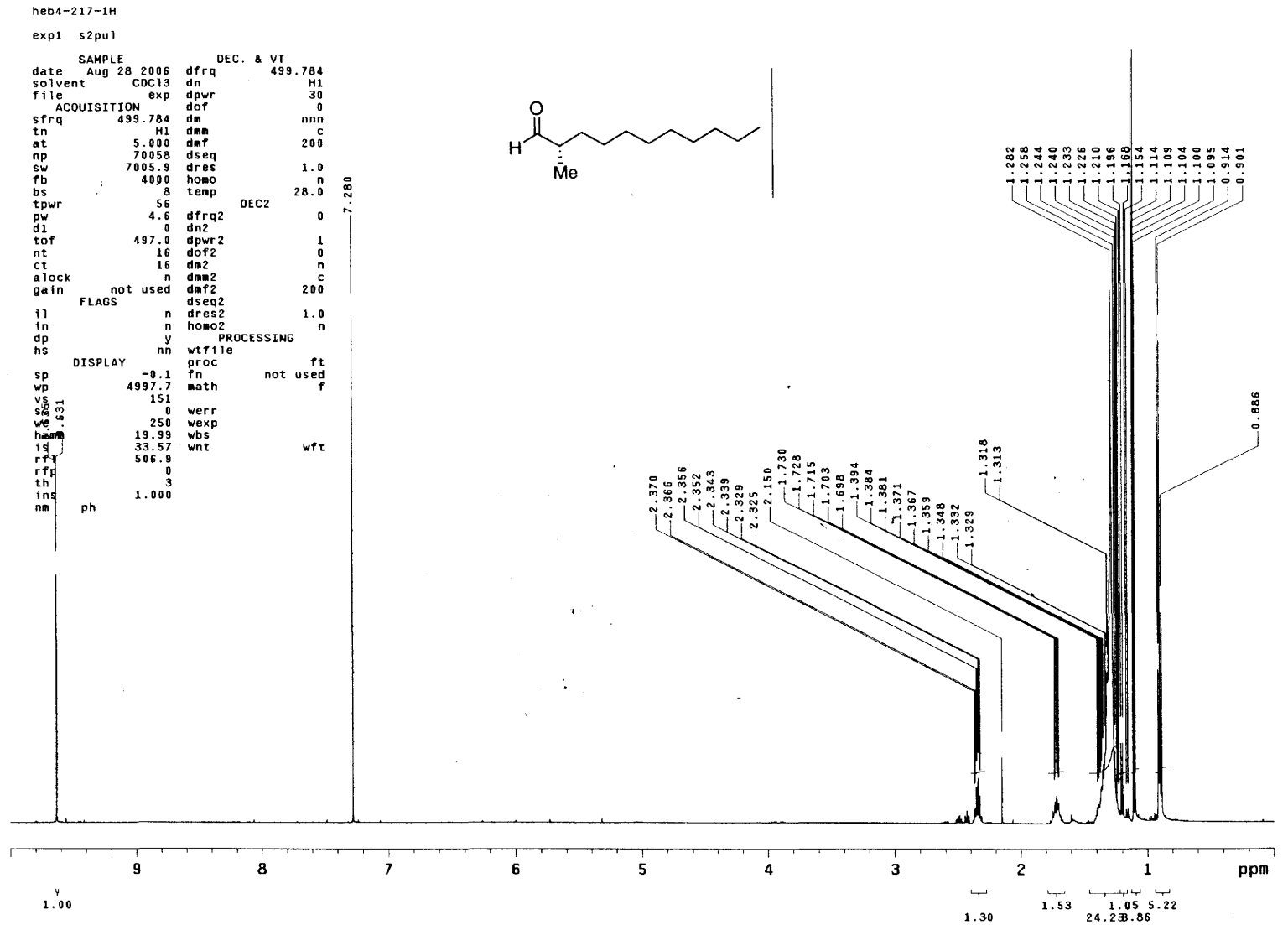


2.27

To a 100-mL round-bottom flask with 4Å molecular sieves was added (*S*)-2-methyl-undecan-1-ol **2.27** (1.020 g, 5.474 mmol) and CH_2Cl_2 (22 mL). To this was added NMO (961.9 mg, 8.211 mmol). The reaction stirred for 15 min at room temperature before TPAP (48.9 mg, 0.1368 mmol) was added under nitrogen. The reaction was complete within 1 h, sieves were removed by filtration over Celite, and solvent was removed by rotary evaporation. The unpurified reaction mixture was purified on a silica plug (8% ethyl acetate/hexanes). (*S*)-2-Methylundecanal was used immediately.



(*S*)-2-Methylundecanal. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 6.9 Hz, C**H**$_3$CH$_2$), 1.12 (3H d, J = 6.9 Hz, C**H**$_3$CHCHO), 1.24-1.39 (14H, m, (C**H**$_2$)$_7$), 1.69-1.73 (2H, m, CHC**H**$_2$), 2.33-2.35 (1H, m, C**H**CH$_2$), 9.63 (1H, d, J = 1.9 Hz, C**H**O). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 14.3, 22.9, 27.2, 29.5, 29.7, 29.8, 29.9, 30.7, 32.1, 46.5, 205.7. IR (neat): 2917 (s), 2854 (s), 1706 (s), 1469 (s), 1381 (m), 1230 (m) cm^{-1}. MS-EI: for $C_{12}H_{23}O$ calc'd: 183.1749 $(M-H)^+$, observed: 183.1742 $(M-H)^+$. Purification: silica gel plug with 8% ethyl acetate/hexanes as the eluant. R_f = 0.76 (10% ethyl acetate/hexanes, stain in PMA).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solvent CDCl3
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1.05
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24.23
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heb4-217-13C

exp1 s2pul

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at	3.000	dmf	11905
np	200168	dseq	
sw	33361.1	dres	1.0
fb	18000	homo	n
bs	32	DEC2	
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ct	896	dmm2	c
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FLAGS		dres2	1.0
il	n	homo2	n
in	n	PROCESSING	
dp	y	lb	1.00
hs	nn	wtfile	
DISPLAY		proc	ft
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wp	33360.9	math	f
vs	162		
sc	0	werr	
wc	250	wexp	
hzmm	133.44	wbs	wft
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th	17		
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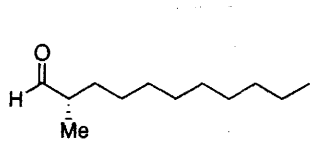
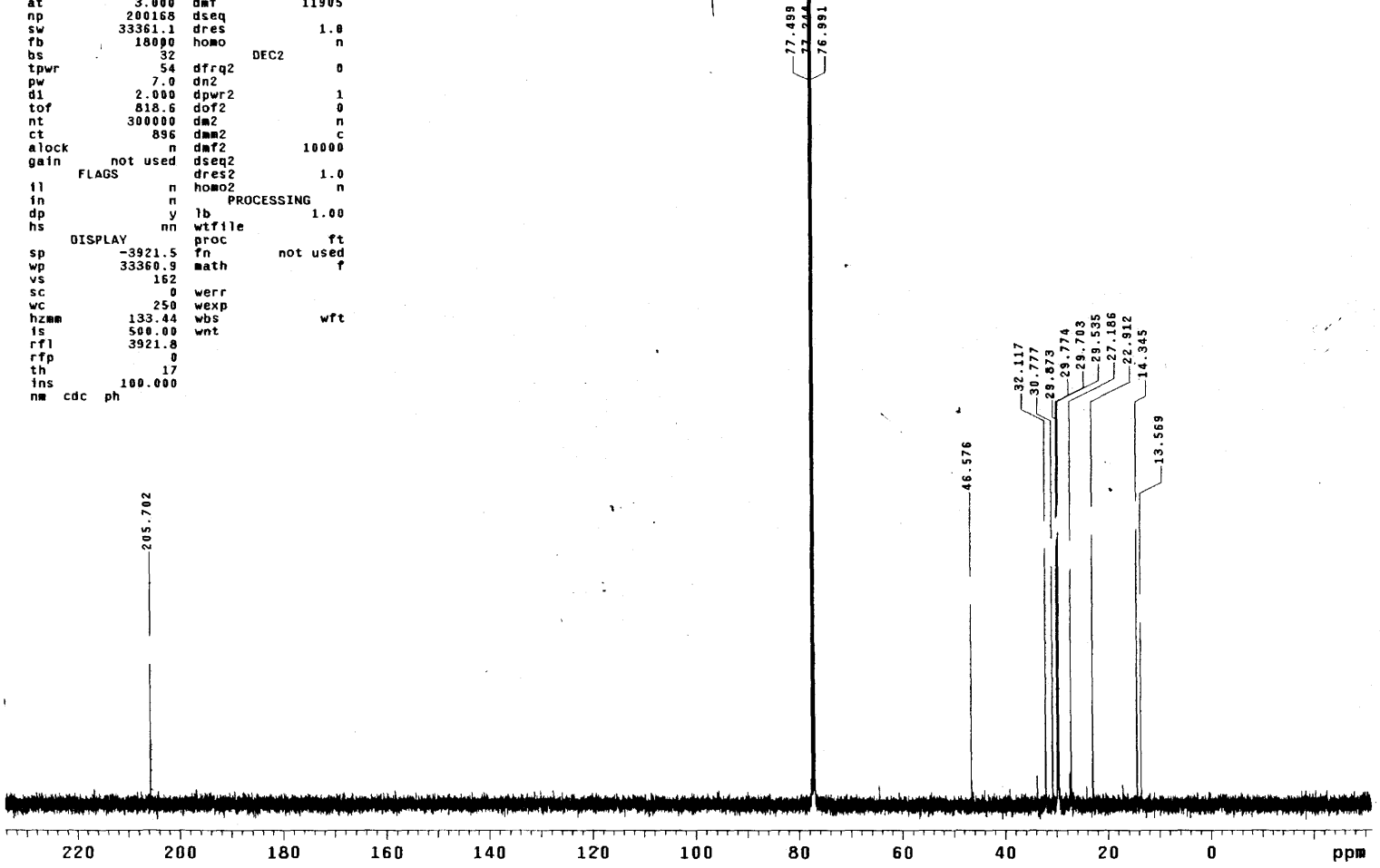
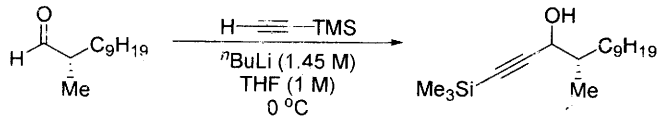
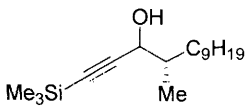
nm	cdc ph		





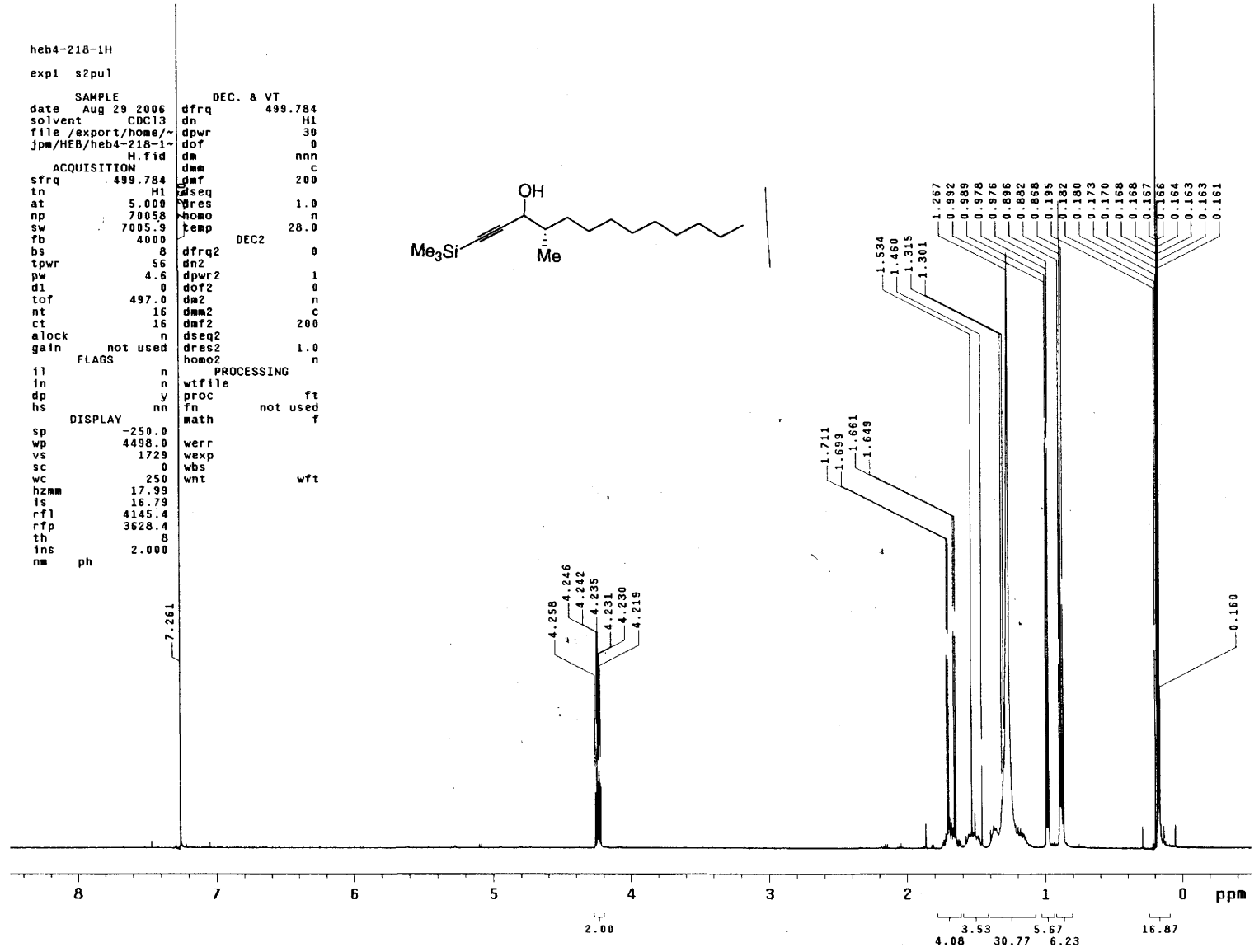


To a 50-mL round-bottom flask was added (trimethylsilyl)acetylene (843 μL, 5.96 mmol) and THF (10.8 mL). The reaction was cooled to 0 °C (ice-water bath) and ^{n}BuLi (1.45 M, 4.1 mL) was added. The reaction stirred for 1 h at 0 °C and it was charged with (*S*)-2-methylundecanal as a solution in THF (5 mL). The reaction stirred at 0 °C for 2 h, when it was diluted with water and ethyl acetate. The aqueous layer was extracted three times with ethyl acetate. The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated. The unpurified reaction mixture was purified on silica gel (2-5% ethyl acetate/hexanes) to afford 886 mg (58% yield, over 2 steps) of (4*S*)-4-methyl-1-(trimethylsilyl)tridec-1-yn-3-ol as a clear oil.



(4*S*)-4-Methyl-1-(trimethylsilyl)tridec-1-yn-3-ol. Diastereomer #1: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.17 (9H, s, $(CH_3)_3Si$), 0.88 (3H, t, J = 7.0 Hz, CH_3CH_2), 0.98 (3H, d, J = 6.5 Hz, CH_3CH), 1.26 (14H, m, br, $(CH_2)_7$), 1.48-1.56 (2H, m, CH_2CH), 1.65 (1H, d, J = 6.0 Hz, $CHCH_3$), 4.21-4.25 (1H, m, HOC**H**), ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.05 (3C), 14.3, 14.8, 22.8, 27.1, 29.5, 29.7, 29.8, 29.9, 32.0, 32.1, 39.3, 67.3, 90.1, 105.6. Diastereomer # 2: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.17 (9H, s, $(CH_3)_3Si$), 0.88 (3H, t, J = 7.0 Hz, CH_3CH_2), 0.98 (3H, d, J = 7.0 Hz, CH_3CH), 1.26 (14H, m, br, $(CH_2)_7$), 1.66-1.72 (2H, m, CH_2CH), 1.70 (1H, d, J = 6.0 Hz, $CHCH_3$), 4.21-4.25 (1H, m, HOC**H**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.05 (3C), 14.3, 15.0, 22.8, 27.2, 29.5, 29.7, 29.8, 29.9, 32.0, 32.6, 39.5, 67.5, 90.5, 106.2. IR (neat): 3345 (s), 2923

(s), 2854 (s), 2168 (s), 1469 (s), 1255 (s) cm^{-1}. HRMS-EI: for $C_{17}H_{33}OSi$ calc'd: 281.2295 $(M-H)^+$, observed: 281.2298 $(M-H)^+$. Purification: silica gel with 5% ethyl acetate/hexanes afforded 886 mg (58% yield, over 2 steps) of (4*S*)-4-methyl-1-(trimethylsilyl)tridec-1-yn-3-ol as a clear oil. R_f = 0.56 (10% ethyl acetate/hexanes, stain in PMA).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heb4-218-13C

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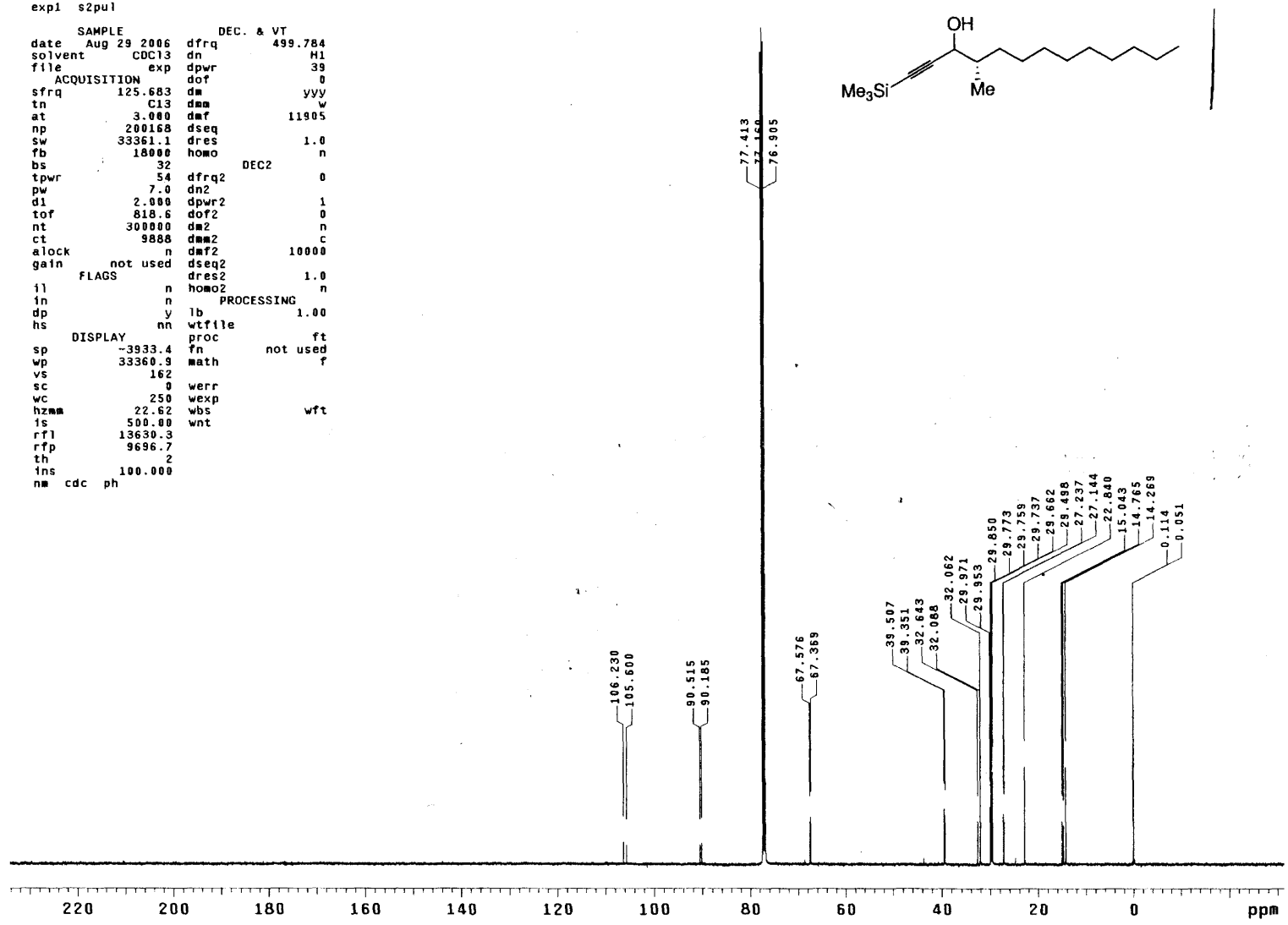
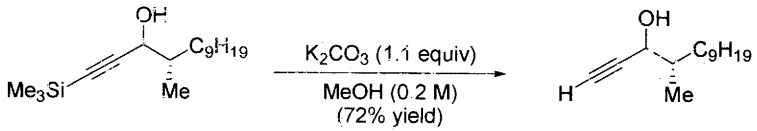
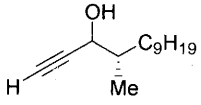


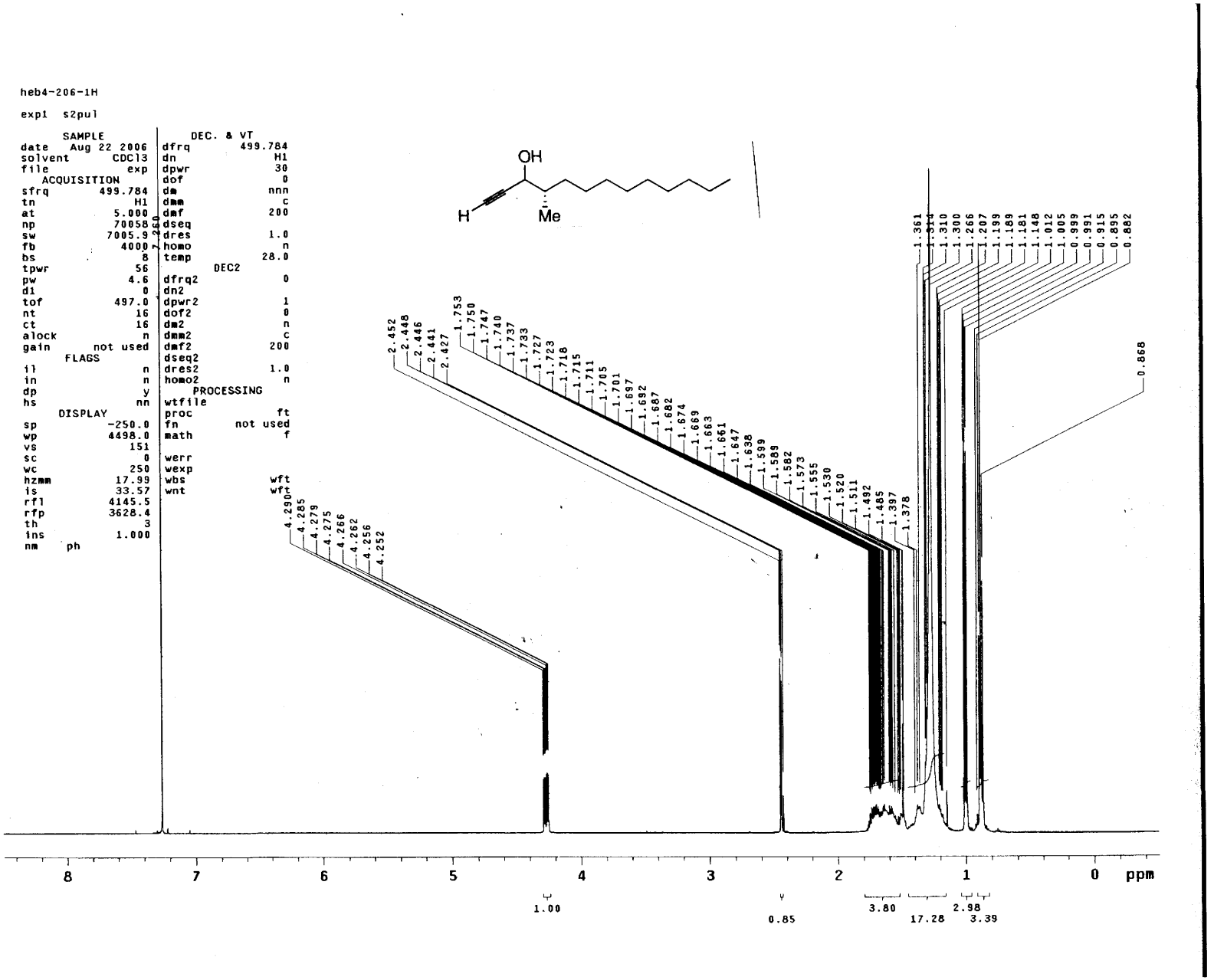


To a 100-mL round-bottom flask was added (4*S*)-4-methyl-1-(trimethylsilyl)tridec-1-yn-3-ol (1.13 g, 3.99 mmol) and methanol (20 mL). Potassium carbonate (607.8 mg, 4.399 mmol) was added under nitrogen and the reaction stirred for 3 h at which it was diluted with water and ethyl acetate. The aqueous layer was washed three times with ethyl acetate and the organic layers were combined and washed with brine. The organic layer was dried ($MgSO_4$) and filtered over Celite. Solvent was removed by rotary evaporation and the unpurified reaction material was purified on silica gel (10% ethyl acetate/hexanes) to afford 606 mg of (4*S*)-4-methyltridec-1-yn-3-ol as a clear oil (72% yield).



(4*S*)-4-Methyltridec-1-yn-3-ol. Diastereomer #1: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 6.5 Hz, $CH_2C\mathbf{H_3}$), 0.99 (3H, d, *J* = 7.0 Hz, $C\mathbf{H_3}CH$), 1.26-1.36 (14H, m, br, $(C\mathbf{H_2})_7$), 1.37-1.48 (2H, m, $CHC\mathbf{H_2}$), 1.52-1.75 (1H, m, $C\mathbf{H}CH_3$), 2.44 (1H, d, *J* = 3.5 Hz, **H**CC), 4.26 (1H, dd, *J* = 5.0, 2.0 Hz, HOC**H**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 14.6, 22.8, 27.1, 29.5, 29.8, 29.9, 30.0, 31.9, 32.6, 39.2, 66.8, 73.6, 83.5. Diastereomer #2: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 6.5 Hz, $C\mathbf{H_3}$), 1.00 (3H, d, *J* = 7.0 Hz, $C\mathbf{H_3}CH$), 1.26-1.36 (14H, m, br, $(C\mathbf{H_2})_7$), 1.37-1.48 (2H, m, $CHC\mathbf{H_2}$), 1.52-1.75 (1H, m, $C\mathbf{H}CH_3$), 2.45 (1H, d, *J* = 3 Hz, **H**CC), 4.28 (1H, dd, *J* = 5.2, 2.2 Hz, HOC**H**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 15.0, 22.8, 27.2, 29.5, 29.8, 29.9, 30.0, 32.0, 32.6, 39.4, 66.9, 73.9, 84.2. IR (neat): 3307 (s), 2923 (s), 2860 (s), 1463

(s), 1381 (s), 1029 (s) cm^{-1}. HRMS-DART (NH_4OH): for $C_{14}H_{30}NO$ calc'd: 228.2327 $(M + NH_4)^+$, observed: 228.2319 $(M + NH_4)^+$. Purification: silica gel with 5% ethyl acetate/hexanes afforded 606 mg (72% yield) of a clear oil. R_f = 0.36 (10% ethyl acetate/hexanes, stain in PMA).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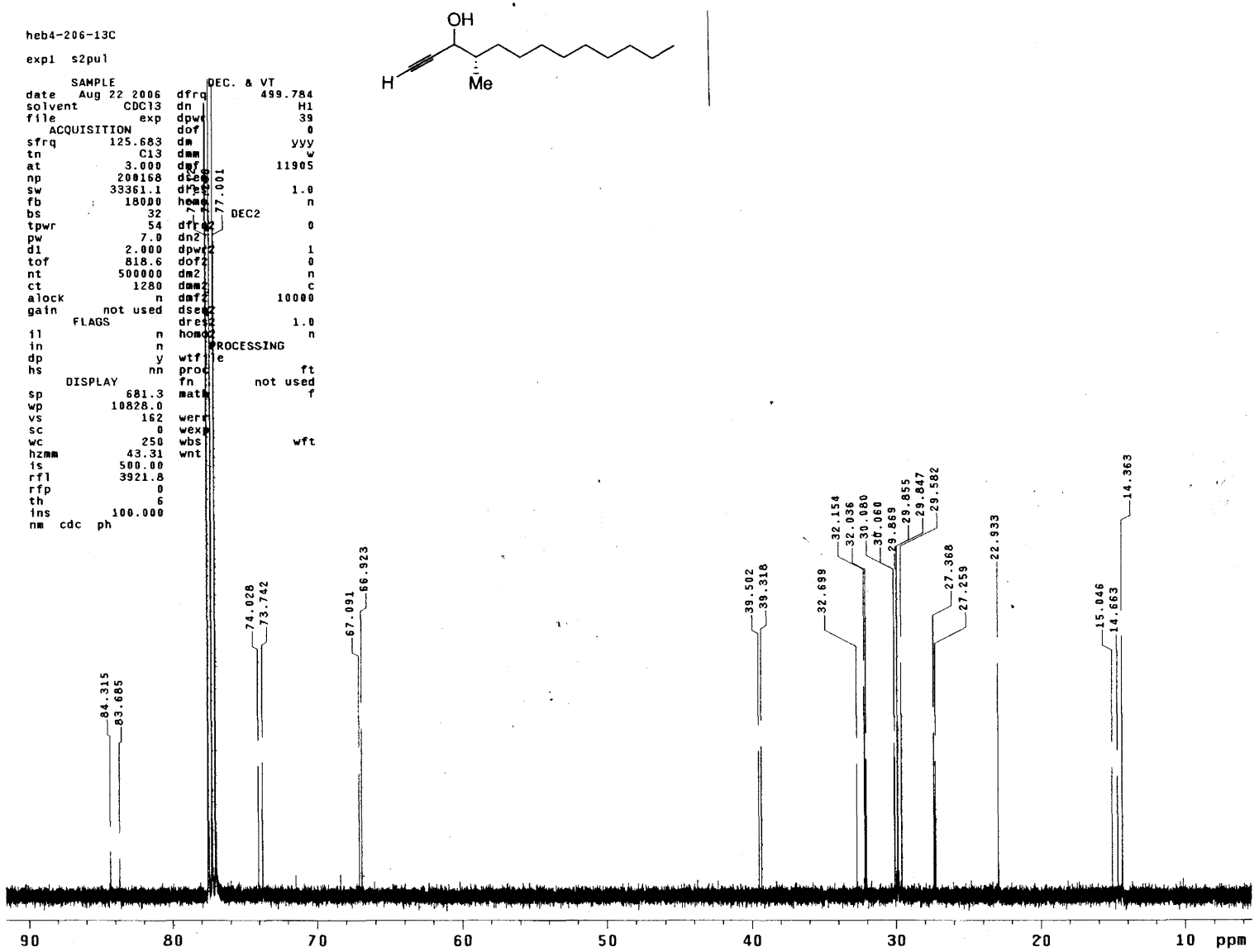
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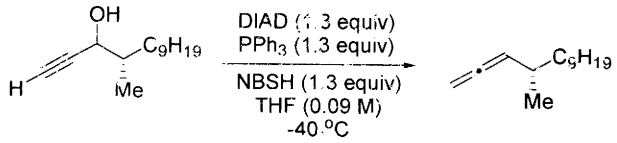
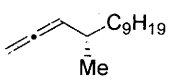


2.25

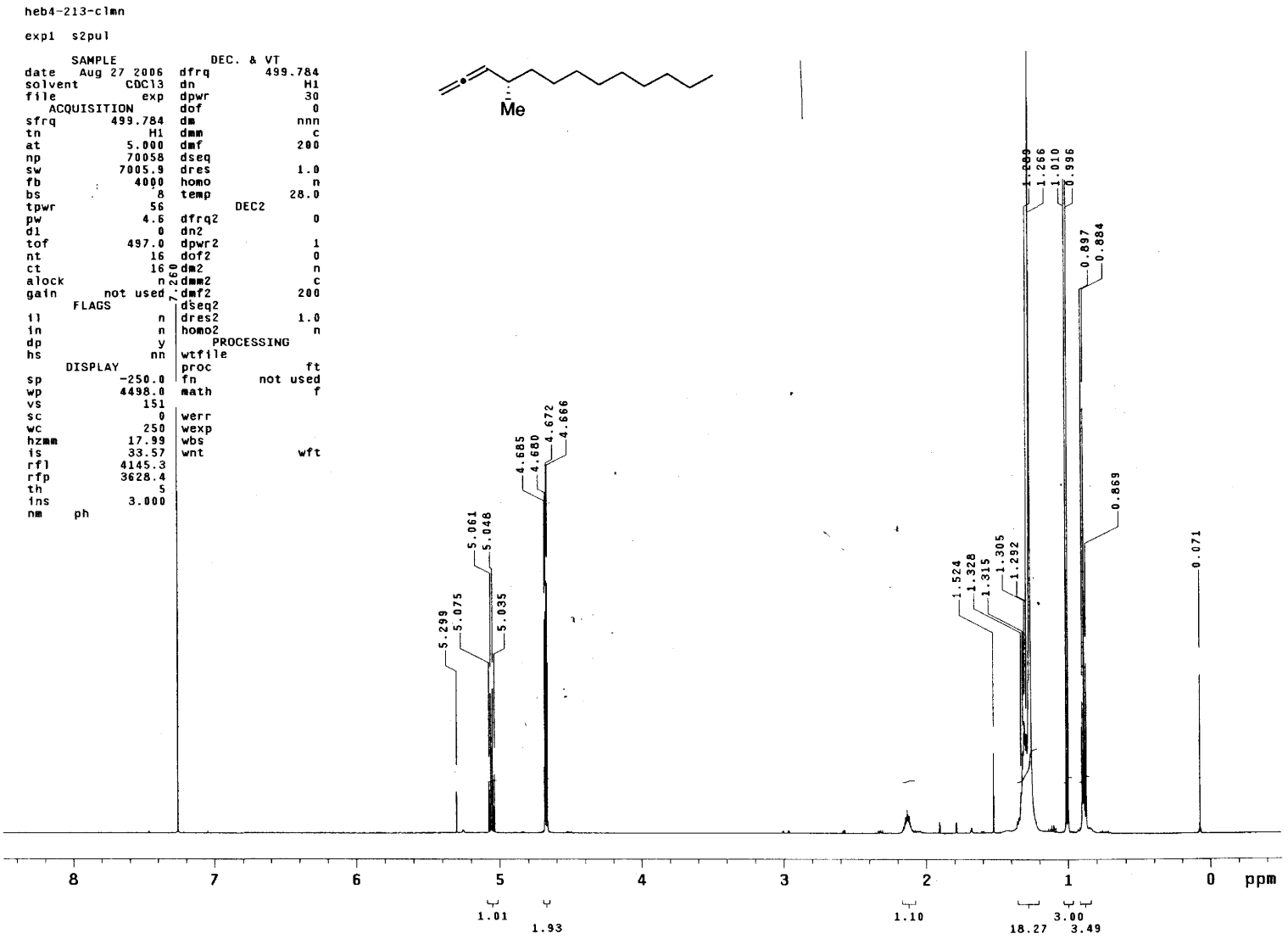
To a 3-neck 100-mL round-bottom flask was added triphenylphosphine (982 mg, 3.74 mmol) and tetrahydrofuran (12 mL, 0.33 M). The flask was cooled to -40 °C (dry ice and ethylene glycol) and diisopropyl azodicarboxylate (737 mL, 3.74 mmol) was added. The reaction mixture stirred at -40 °C for 15 min, when (*S*)-4-methyl-tridec-1-yn-3-ol (606 mg, 2.88 mmol) in tetrahydrofuran (9 mL) was transferred by cannula into the reaction mixture. After an additional 15 min at -40 °C, *o*-nitrobenzenesulfonylhydrazine (813 mg, 3.74 mmol) in tetrahydrofuran (12 mL) was transferred by cannula into the reaction. After 2 h at -40 °C, the reaction was slowly warmed to ambient temperature and stirred overnight. The unpurified reaction mixture was concentrated on a rotovap and purified on silica gel (pentanes) to afford 230 mg (83% ee, 41% yield) of a clear oil. GLC analysis of the reaction product is illustrated in section 2.5.9.1.



2.25

(*S*)-4-Methyl-trideca-1,2-diene (2.25). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.0 Hz, CH_3CH_2), 1.00 (3H, d, J = 7.0 Hz, CH_3CH), 1 26-1.32 (14H, m, br, $(CH_2)_7$), 2.10-2.15 (1H, m, $CHCH_3$), 4.66 (2H, dd, J = 7.0, 3.0 Hz, H_AH_BC), 5.05 (1H, q, J = 7.0 Hz, $CHCCCH_2$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 20.5, 22.8, 27.3, 29.5, 29.7, 29.8, 29.9, 32.0, 33.0, 37.3, 75.4, 96.3, 207.6. IR (neat): 2961 (s), 2936 (s), 2860 (s), 1954 (m), 1463 (m), 840 (m) cm^{-1}. HRMS-EI: for $C_{14}H_{26}$

calc'd: 194.2029 (M+), observed: 194.2034 (M+). Purification: silica gel with pentanes afforded 230 mg (41% yield) of a clear oil. R_f = 0.90 (pentanes, stain in $KMnO_4$).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heb4-213-13C

expl s2pul

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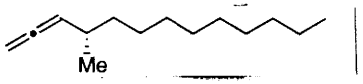
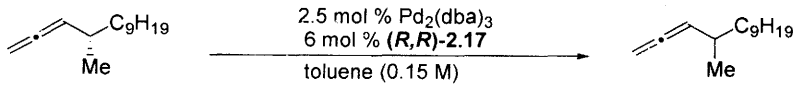
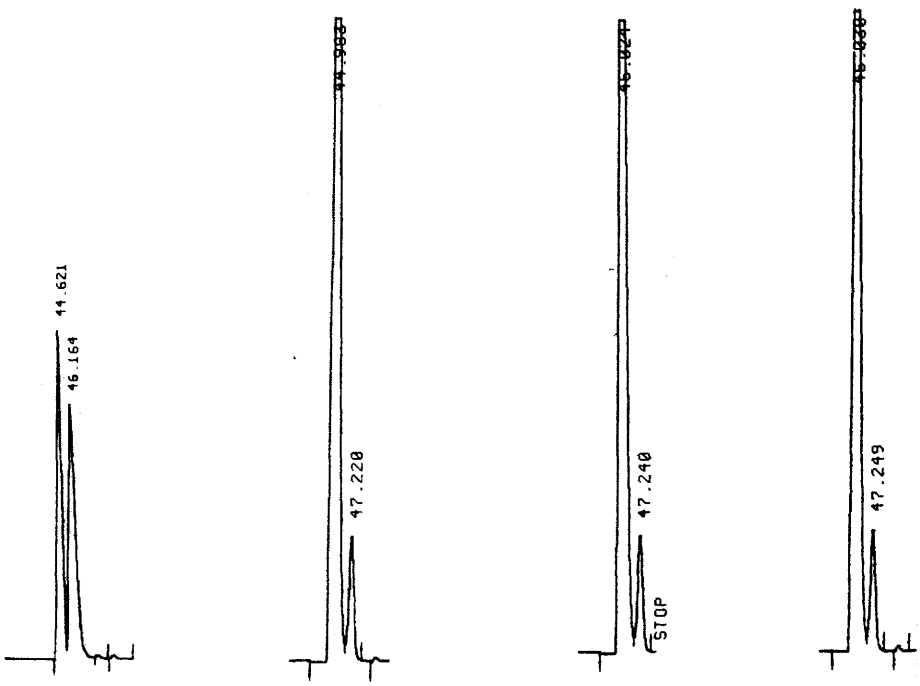




2.5.10.1. Racemization Experiment with (S)-4-Methyl-trideca-1,2-diene 2.25. In the dry box, to a 6-dram vial was added $Pd_2(dba)_3$ (5.8 mg, 0.0064 mmol) and **(*R,R*)-2.17** (10.0 mg, 0.154 mmol) in toluene (1.71 mL). The metal and ligand were allowed to complex for 1 h when **2.25** (50 mg, 0.2572 mmol) was added. The reaction mixture was removed from the glove box and stirred for 1 h when solvent was removed *in vacuo*. The unpurified reaction mixture was purified on a silica gel plug (pentanes) and 38.2 mg (76%) of (*S*)-4-methyl-trideca-1,2-diene was recovered and analyzed by chiral GLC. There was no indication of racemization observed after a reaction time of 1 h. The procedure was repeated with a reaction time of 16 h and racemization was not observed.

Chiral GLC (β-dex, Supelco, 95 °C) – analysis of (S)-4-methyl-trideca-1,2-diene.



Racemic **(*S*)-2.25** **(*S*)-2.25** **(*S*)-2.25**

at time = 1 h at time = 16 h

2.5.11. Kinetic Studies for Allene Diboration

2.5.11.1. Preparation of capillary tubes containing 1,3-dimethoxybenzene. A stock solution of 1,3-dimethoxybenzene (100 μL, 0.7635 mmol) in toluene-d_8 (5 mL) was prepared. A 6-inch 22 gauge needle attached to a 100 μL gas-tight syringe was used to transfer 70 μL of the stock solution to a capillary tube. Each capillary was flame-sealed and its accuracy checked by ^{1}H NMR against a stock solution of tridec-1,2-diene.

2.5.11.2. Initial Rate Studies with varied [$B_2(pin)_2$].

Preparation of stock solutions. All operations were performed in the dry box, all glassware was oven-dried overnight prior to use, and gas-tight microliter syringes were used for all operations. Stock solutions were prepared immediately before use.

Tridec-1,2-diene solution: To a 6-dram vial was added 405.3 mg (2.247 mmol) of tridec-1,2-diene and this was diluted with toluene-d_8 (1.5 mL).

Catalyst solution: To a 6-dram vial was added $Pd_2(dba)_3$ (11.8 mg, 0.0128 mmol), **(*R*,*R*)-2.17** (18.8 mg, 0.0288 mmol), and toluene-d_8 (4 mL). This mixture was allowed to incubate for 1 h prior to use.

$B_2(pin)_2$ solution: To a 6-dram vial was added bis(pinacolato)diboron (457.7 mg, 1.802 mmol) and toluene-d_8 (3 mL).

Kinetic Runs:

[$B_2(pin)_2$] = 0.45 M: To a J-Young tube was added 200 μL of the catalyst solution. To this was added 100 μL of toluene-d_8 and 1.5 mL of $B_2(pin)_2$ solution. The J-Young tube

was sealed with a Teflon cap and inverted several times. The Teflon cap was removed, the flame-sealed capillary inserted, and 200 μL of tridec-1,2-diene solution was added. The J-Young tube was sealed with the Teflon cap and inverted several more times.

$[B_2(pin)_2]$ = 0.30 M: This experiment was conducted as above except that 1 mL of $B_2(pin)_2$ solution and 600 μL of toluene were employed.

$[B_2(pin)_2]$ = 0.15 M: This experiment was conducted as above except that 0.5 mL of $B_2(pin)_2$ solution and 1.1 mL of toluene were employed.

Results. Single-pulse ^1H NMR was utilized to measure the formation of product (in comparison to the internal standard) versus time.

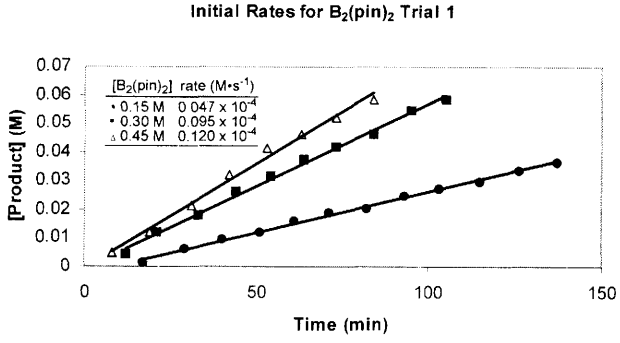


Figure 2.S1. Initial Rates for $B_2(pin)_2$ Trial 1: Catalyst Loading: 0.2 mol % $Pd_2(dba)_3$ and 0.48 mol % ***(R,R)*-2.17**

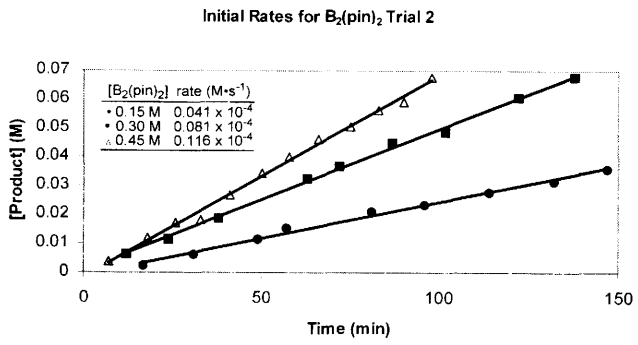


Figure 2.S2. Initial Rates for $B_2(pin)_2$ Trial 2: Catalyst Loading: 0.2 mol % $Pd_2(dba)_3$ and 0.48 mol % ***(R,R)*-2.17**

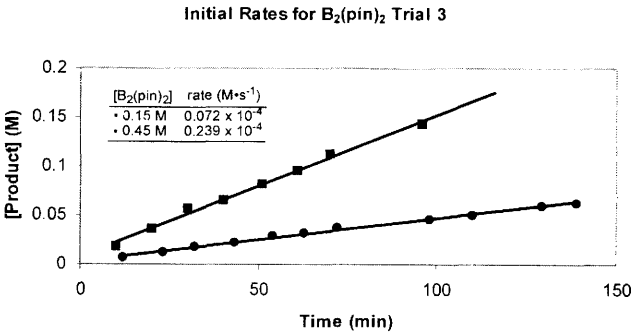


Figure 2.S3. Initial Rates for $B_2(pin)_2$ Trial 3: Catalyst Loading: 0.5 mol % Pd_2dba_3 and 1.2 mol % ***(R,R)*-2.17**

2.5.11.3. Initial Rate Studies with varied [Allene].

Preparation of stock solutions. All operations were performed in the dry box, all glassware was oven-dried overnight prior to use, and gas-tight microliter syringes were used for all operations. Stock solutions were prepared immediately before each kinetic run.

Tridec-1,2-diene solution: To a 6-dram vial was added 324.4 mg (1.799 mmol) of tridec-1,2-diene and this was diluted with toluene-d_8 (3 mL).

Catalyst solution: To a 6-dram vial was added $Pd_2(dba)_3$ (12.0 mg, 0.0131 mmol), **(*R*,*R*)-2.17** (19.8 mg, 0.0303 mmol), and toluene-d_8 (4 mL). The metal and ligand were incubated for 1 hour in the dry box prior to use.

$B_2(pin)_2$ solution: To a 6-dram vial was added bis(pinacolato)diboron (571.0 mg, 2.248 mmol) and toluene-d_8 (1.5 mL).

Kinetic Runs:

[tridec-1,2-diene] = 0.45 M: To a J-Young tube was added 200 μL of the catalyst solution. To this was added 100 μL of toluene-d_8 and 200 μL of $B_2(pin)_2$ solution. The J-Young tube was sealed with a Teflon cap and inverted several times. The Teflon cap was removed, the flame-sealed capillary inserted, and 1.5 mL of tridec-1,2-diene solution was added. The J-Young tube was sealed with the Teflon cap and the NMR tube inverted several more times.

[tridec-1,2-diene] = 0.30 M: This was carried out as above except that 1 mL of the tridec-1,2-diene solution and 600 μL of toluene were used.

[tridec-1,2-diene] = 0.15 M: This was carried out as above except that 0.5 mL of the tridec-1,2-diene solution and 1.1 mL of toluene were used.

Results. Single-pulse ^{1}H NMR was utilized to measure the formation of product (in comparison to the internal standard) versus time.

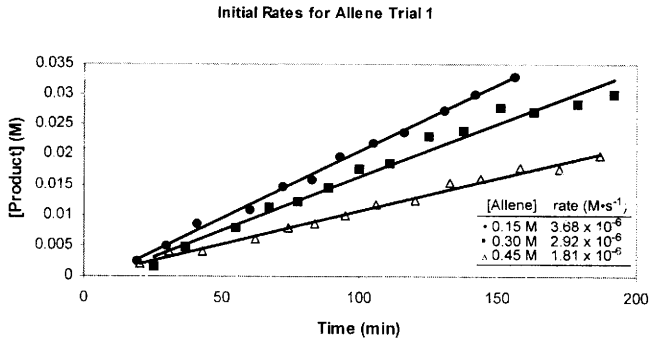


Figure 2.S4. Initial Rates for Tridec-1,2-diene Trial 1: Catalyst Loading: 0.2 mol % $Pd_2(dba)_3$ and 0.48 mol % ***(R,R)*-2.17**

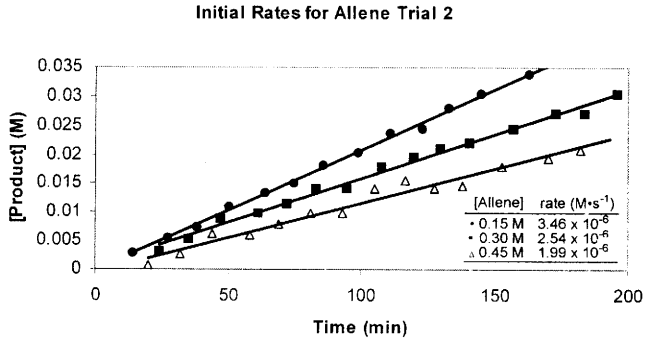


Figure 2.S5. Initial Rates for Tridec-1,2-diene Trial 2: Catalyst Loading: 0.2 mol % $Pd_2(dba)_3$ and 0.48 mol % ***(R,R)*-2.17**

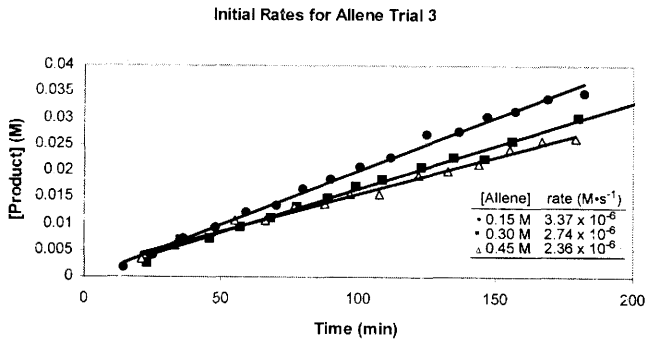


Figure 2.S6. Initial Rates for Tridec-1,2-diene Trial 3: Catalyst Loading: 0.2 mol % $Pd_2(dba)_3$ and 0.48 mol % ***(R,R)*-2.17**

Chapter 3

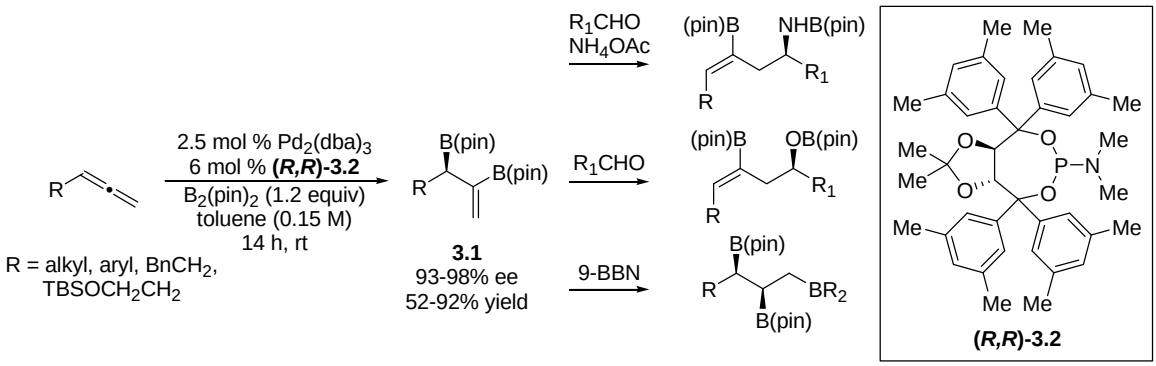
Asymmetric Synthesis and Functionalization of 1,4-Bis(boronate)esters

3.1. Introduction

In 2004, the Morken lab reported the first enantioselective diboration of prochiral allenes to form chiral 1,2-bis(boronate)esters in up to 92% ee.[1] The palladium/TADDOL-phosphoramidite catalyst was further optimized, and the enantioselectivity of 1,2-bis(boronate)ester (**3.1**) formation was increased to 98% ee (Scheme 3.1).[2] The synthetic utility of α-chiral 1,2-bis(boronate)esters **3.1** has been demonstrated in tandem diboration/allylation[2a,3] or diboration/hydroboration[4] reaction sequences.

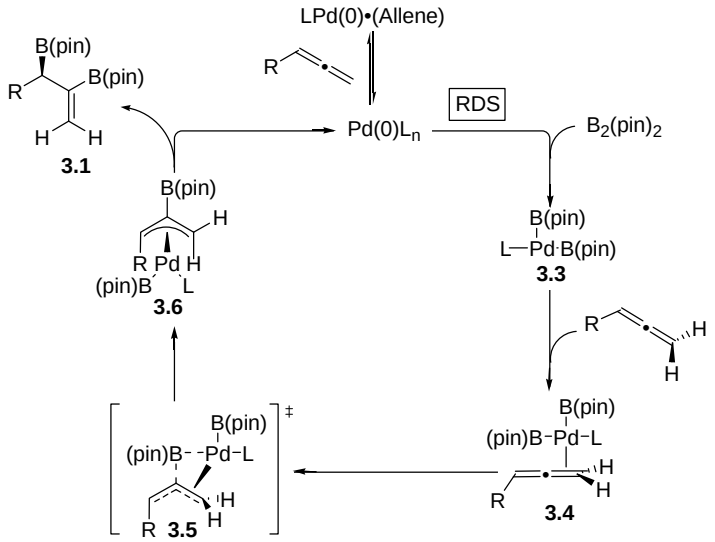
(1) Pelz, N. F.; Woodward, A. R.; Burks, H. E.; Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 16328.
(2) (*a*) Woodward, A. R.; Burks, H. E.; Chan, L. M.; Morken, J. P. *Org. Lett.* **2005**, *7*, 5505. (*b*) Burks, H. E.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 8766.
(3) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2006,** *128*, 74.
(4) Pelz, N. F.; Morken, J. P. *Org. Lett.* **2006**, *8*, 4557.

Scheme 3.1. Pd-Catalyzed Enantioselective Allene Diboration



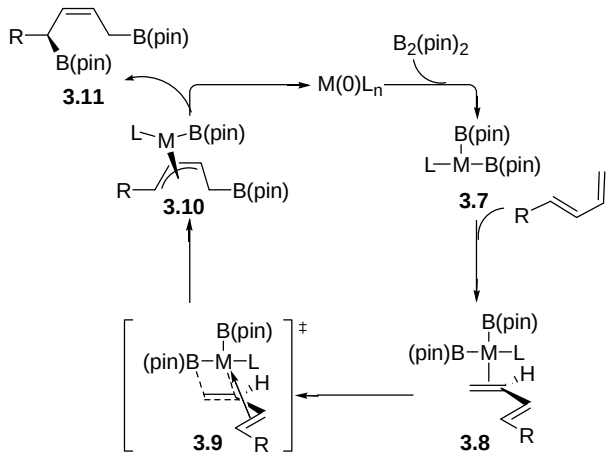
The reaction mechanism for the Pd-catalyzed allene diboration is depicted in Scheme 3.2. Support for this mechanism was garnered from several experiments, coupled with DFT calculations (see Chapter 2). Rate-determining oxidative addition of $B_2(pin)_2$ to Pd(0) forms Pd-bis(boryl) adduct **3.3**, which coordinates to the terminal bond of the allene (**3.4**). Substrate insertion into **3.3** occurs through a single transition state (**3.5**) where carbon-boron bond formation occurs concomitantly with the development of the π-allyl complex **3.6**. Reductive elimination from **3.6** delivers the desired 1,2-bis(boronate)ester **3.1**.

Scheme 3.2. Mechanism for the Pd-Catalyzed Asymmetric Allene Diboration



An enantioselective transition-metal-catalyzed diene diboration should proceed by an analogous reaction mechanism (Scheme 3.3). The coordination of oxidative addition adduct (**3.7**) to the substrate can occur at the terminal bond of the diene (**3.8**). Similar to allene diboration, the transition state for the insertion should be stabilized by coordination of the adjacent olefin of the diene to the transition metal; this would require the diene to be in the *s-cis* conformation. Thus, diene insertion should proceed through a single transition state (**3.9**) where carbon-boron bond formation occurs with the development of the π-allyl complex. Reductive elimination from π-allyl intermediate **3.10** should afford either the α-chiral 1,4-bis(boronate)ester **3.11** or the 1,2-bis(boronate)ester (not shown).

Scheme 3.3. Mechanism for the Transition-Metal-Catalyzed Diboration of Dienes

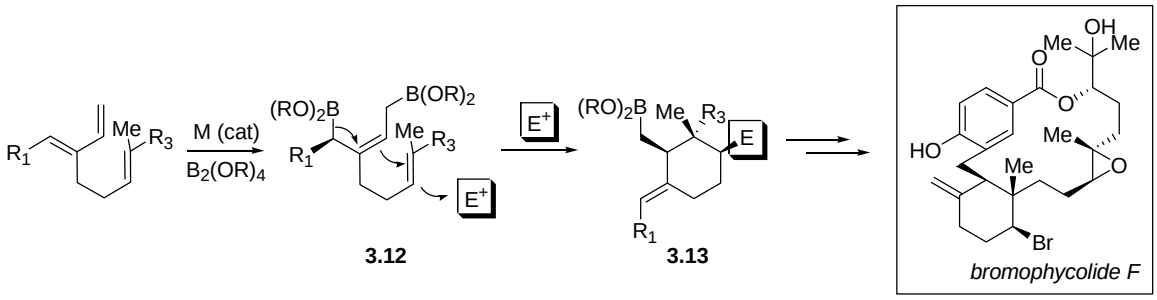


The practical application of 1,4-bis(boronate)esters like **3.11** could be extended beyond traditional allylation reactions, which generally employ allyl boronates. The development of new reaction sequences that utilize α-chiral allylboronates such as **3.12** would expedite the total synthesis of complex molecules such as bromophycolide F (Scheme 3.4).[5] The core structure **3.13** of bromophycolide F can easily obtained from an electrophile-induced cyclization of 1,4-bis(boronate)ester **3.12**. Chirality transfer from the optically enriched 1,4-bis(boronate)ester **3.12** would deliver an enantioselective synthesis of the core.[6]

(5) For the isolation of bromophycolide F, see: (*a*) Kubanek, J.; Prusak, A. C.; Snell, T. W.; Giese, R. A.; Fairchild, C. R.; Aalbersberg, W.; Hay, M. E. *J. Nat. Prod.* **2006,** *69*, 731. (*b*) Kubanek, J.; Prusak, A. C.; Snell, T. W.; Giese, R. A.; Hardcastle, K. I.; Fairchild, C. R.; Aalbersberg, W.; Raventos-Suarez, C.; Hay, M. E. *Org. Lett.* **2005,** *7*, 5261.

(6) For examples of enantioselective halocyclization reactions, see: (*a*) Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900. (*b*) Garnier, J. M.; Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2007**, 3281. (*c*) Grossman, R. B.; Trupp, R. J. *Can. J. Chem.* **1998**, *76*, 1233. (*d*) Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Tetrahedron Lett.* **1992**, *33*, 46, 6999. (*e*) Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *J. Chem. Soc., Chem. Commun.* **1992**, *9*, 728. (*f*) Kitagawa, O.; Hanano, T.; Tanabe, K.; Shiro, M.; Taguchi, T. *J. Chem. Soc., Chem. Commun.* **1992**, 1005.

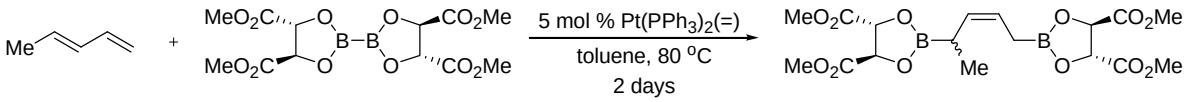
Scheme 3.4. Electrophile-Induced Cyclization of α-Chiral Allyl Boronate **3.12**



3.2. Background

The first report of the addition of diboron reagents to dienes was disclosed by Miyaura.[7] Subsequent investigations by Marder[8] and Morken[9] have expanded the scope and synthetic utility for diene diboration, but not the enantioselectivity. The only source of selectivity achieved thus far employed chiral ligands on boron, and the levels are low.[8] Platinum-catalyzed addition of bis(tartrate glycolato)diboron to *trans*-piperylene afforded 1,4-bis(boronate)ester **3.14** in 20% d.e. (Scheme 3.5). Therefore, the need exists to develop an efficient enantioselective synthesis of 1,4-bis(boronate)esters.

Scheme 3.5. Marder's Pt-Catalyzed Diene Diboration with Chiral Ligands on Boron



3.14
70% yield, 20% d.e.

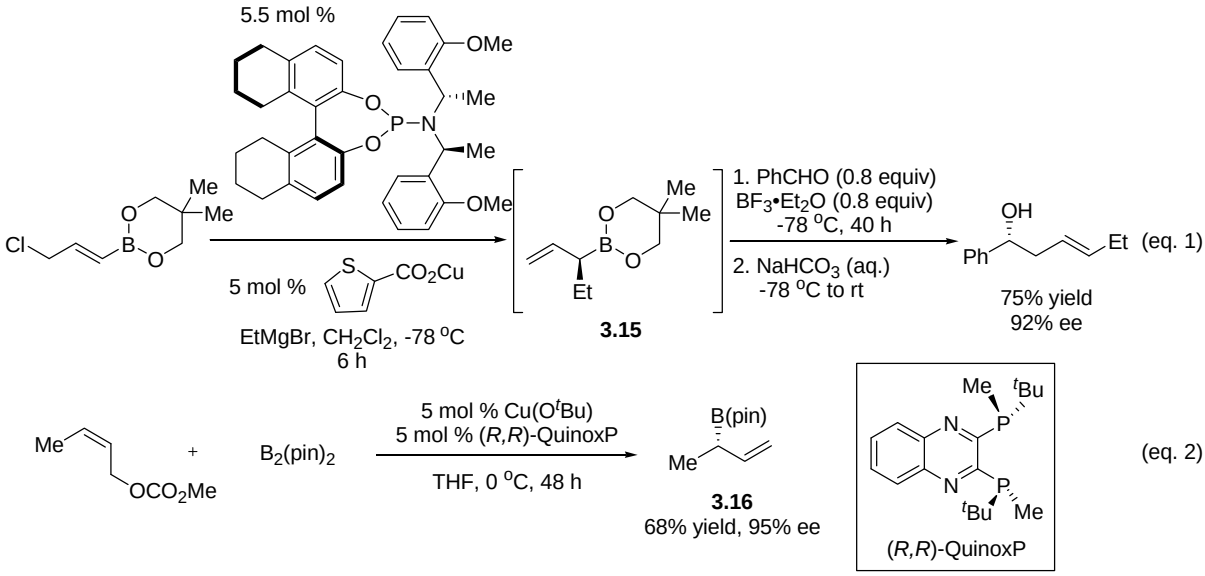
The highly versatile organoboron intermediates,[10] may allow for rapid access to molecularly-complex structures. Until recently, very few synthetic transformations have

(7) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Comm.* **1996,** *17*, 2073.
(8) Clegg, W.; Johann, T. R. F.; Marder, T. B.; Norman, N. C.; Orpen, A. G.; Peakman, T. M.; Quayle, M. J.; Rice, C. R.; Scott, A. J. *J. Chem. Soc., Dalton Trans.* **1998,** 1431.
(9) (*a*) Ballard, C. E.; Morken, J. P. *Synthesis* **2004**, 1321. (*b*) Morgan, J. B.; Morken, J. P. *Org. Lett.* **2003**, *5*, 2573.
(10) Brown, H. C.; Singaram, B. *Pure Appl. Chem.* **1987**, *59*, 879.

been reported with α-chiral allylboronates, and these are mostly limited to aldehyde allylation. The synthesis of α-chiral allylboronates was pioneered by Hoffmann,[11] with recent advances from the laboratories of Matteson,[12] Hall,[13] Pietruszka,[14] Aggarwal,[15] and Sawamura.[16] Hall has recently reported a copper-catalyzed synthesis of α-chiral allylboronate **3.15** from ethyl magnesium bromide addition to 3-chloropropenylboronates (Scheme 3.6, eq. 1). Lewis acid-catalyzed allylation of benzaldehyde with **3.15** delivered the homoallylic alcohol 92% ee. Only primary aliphatic Grignard reagents afforded α-chiral allylboronates in high yield. Secondary aliphatic Grignard reagents produced the α-chiral allylboronates in low yield. In a recent report by Sawamura, an enantioselective copper-catalyzed synthesis of α-chiral allylboronate **3.16** from allyl carbonates was disclosed (Scheme 3.6, eq. 2). This transformation proceeded in high yields and enantioselectivities for all substrates examined. However, the substrate scope was limited to primary aliphatic allyl carbonates.

Scheme 3.6. Enantioselective Synthesis of α-Chiral Allylboronates

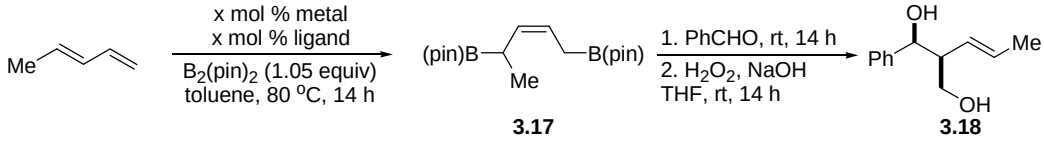
(11) (*a*) Hoffmann, R. W. *Pure Appl. Chem.* **1988**, *60*, 123. (*b*) Hoffmann, R. W.; Niel, G.; Schlapbach, A. *Pure Appl. Chem.* **1990**, *62*, 1993.
(12) Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555.
(13) (*a*) Carosi, L.; Hall, D. G. *Angew. Chem. Int. Ed.* **2007**, *46*, 5913. (*b*) Peng, F.; Hall, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 3070. (*c*) Peng, F.; Hall, D. G. *Tetrahedron Lett.* **2007**, 3305. (*d*) Gao, X.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 9308. (*e*) Gao, X.; Hall, D. G.; Deligny, M.; Favre, A.; Garreaux, F.; Carboni, B. *Chem. Eur. J.* **2006**, *12*, 3132.
(14) (*a*) Pietruszka, J.; Schone, N. *Eur. J. Org. Chem.* **2004**, 5011. (*b*) Pietruszka, J.; Schone, N. *Angew. Chem. Int. Ed.* **2003**, *42*, 5638.
(15) Fang, G. Y.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2007**, *46*, 359.
(16) (*a*) Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034. (*b*) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856.



3.3. Results and Discussion

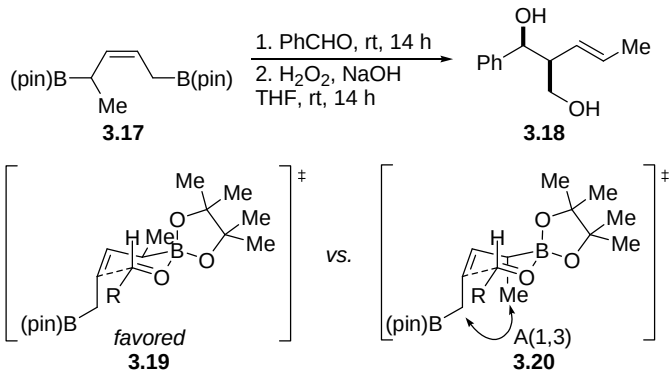
3.3.1. Reaction Development. The asymmetric diene diboration was developed with readily available *trans*-piperylene (Scheme 3. 7). While 1,4-bis(boronate)ester **3.17** may be purified by column chromatography, we believed that the subsequent one-pot allylation and oxidation cascade would facilitate the analysis of catalyst reactivity as well as enantioselectivity.

Scheme 3.7. Transition-Metal-Catalyzed Diene Diboration



A high level of chirality transfer was achieved in the aldehyde allylation with chiral 1,2-bis(boronate)esters derived from allene diboration. A similar level of chirality transfer should be achieved in allylations with chiral 1,4-bis(boronate)ester **3.17**. Two closed-chair transition states can be described for this allylation reaction (Scheme 3.8). In transition state **3.19**, the methyl group of 1,4-bis(boronate)ester **3.17** is oriented in the equatorial position, alleviating a penalizing 1,3-diaxial interaction that is present when this substituent is oriented in the axial position (**3.20**).

Scheme 3.8. Transition States for Allylation with 1,4-Bis(boronate)ester **3.17**

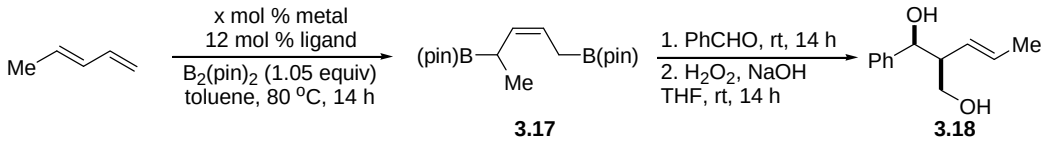


The previously-described Pd-catalyst, effective for promoting the diboration of allenes, was initially surveyed for diene diboration (Table 3.1). While the Pd(0)-catalyst was not effective in promoting the diboration of *trans*-piperylene, platinum(0) catalyzes the dimetallation of alkynes,[17] alkenes,[18] allenes,[19] and dienes-both $Pt(PPh_3)_4$ and $Pt_2(dba)_3$ were surveyed in this reaction. Diboration of *trans*-piperylene proceeded effectively with $Pt(PPh_3)_4$ and $Pt_2(dba)_3/PCy_3$ (entries 3 and 5). The formation of the

(17) Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc.* **1993**, *115*, 11018.
(18) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun.* **1997**, 689.
(19) Ishiyama, T.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1998**, *39*, 2357.

desired *syn*-1,3-diol **3.18** with $Pt_2(dba)_3/PCy_3$ left ample potential for the development of an asymmetric diene diboration due to the large number of chiral phosphorus based ligands available.

Table 3.1. Transition-Metal Catalyst Selection for Asymmetric Diene Diboration

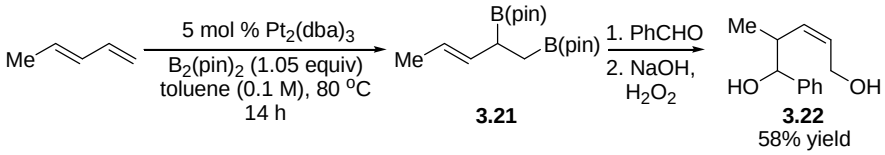


entry	metal (x mol %)	ligand	% yield
1	$Pd_2(dba)_3$ (5%)	PCy_3	0
2	$Pd_2(dba)_3$ (5%)	**(*R*,*R*)-3.2**	0
3	$Pt(PPh_3)_4$ (3%)	-	60
4	$Pt_2(dba)_3$ (5%)	PPh_3	40
5	$Pt_2(dba)_3$ (5%)	PCy_3	66

As alluded to in earlier chapters, "ligand-free" platinum-catalyzed diboration has been documented.[20] Perhaps such observations have dissuaded anyone from pursuing the development of the asymmetric platinum-catalyzed diene diboration, due to the anticipated background reaction with the "ligand-free" catalyst. However, ligand-free platinum-catalyzed diboration of *trans*-piperylene delivered 1,2-bis(boronate)ester **3.21**; after the allylation and oxidation of **3.21**, 1,5-diol **3.22** was formed in 58% yield (Scheme 3.9). *Because an alternative reaction product is formed from the ligand-free pathway, the enantiopurity of the desired reaction product would not be eroded from racemic product typically formed from the background reaction.*

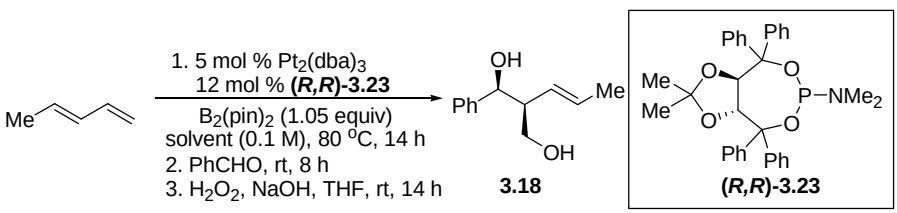
(20) Iverson, C. N.; Smith, M. R., III, *Organometallics* **1997**, *16*, 2757.

Scheme 3.9. Ligand-Free Pt-Catalyzed Diene Diboration



3.3.2. Ligand Selection. The parent TADDOL-derived phosphoramidite **(*R,R*)-3.23**, which delivered allene diboration products in high yield and enantioselectivity, was initially investigated as the chiral ligand for this transformation (Table 3.2). The formation of desired 1,3-diol **3.18** was accomplished in good yields and modest levels of enantioselectivity. With THF as the solvent, the 1,3-diol was formed in the highest enantiopurity (entry 3). The highest level of preference for formation of 1,4-bis(boronate)ester **3.17** was observed in toluene. A possible explanation for this preference is that THF could coordinate to platinum, as opposed to the chiral ligand, and promote the ligand-free pathway which delivered 1,2-bis(boronate)ester **3.21**.

Table 3.2. Solvent Study with TADDOL-Phosphoramidite **(*R,R*)-3.23**

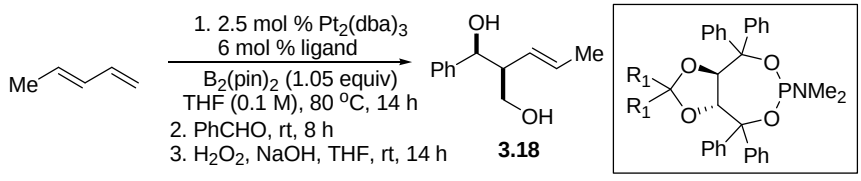


entry	solvent	% yield (% ee)[b]
1	toluene	67 (42)
2	benzene	69 (39)
3	THF	49 (49)

[a] Ratio of 1,4- to 1,2-bis(boronate)ester determined by the crude ^{1}H NMR ratio of the 1,4-diboration/allylation/oxidation product to the 1,2-diboration/allylation/oxidation product. [b] Isolated yield of the 1,3-diol after silica gel chromatography. Enantiomeric excess determined by chiral GLC analysis of the 1,3-diol protected as the dimethyl ketal.

The phosphoramidite scaffold was then modified to increase the enantioselectivity of the asymmetric diene diboration. The parent TADDOL-derivative, featuring a dimethyl ketal, afforded the desired product in 49% ee (Table 3.3, entry 1). Decreasing the steric encumberance of the ketal moiety by employing the formaldehyde dioxalane ring, ligand **(*R,R*)-3.24**, resulted in a minor reduction of enantioselectivity (entry 2). Substitution of R_1 with a larger cyclohexyl ketal, ligand **(*R,R*)-3.25**, afforded nearly racemic product (entry 3). The reduction in enantioselectivity by modification of the ketal moiety of the ligand was surprising. While the ketal impacts the orientation of aryl groups on the TADDOL-backbone, and subsequently influences how phosphorus binds to the transition metal, one would expect a minimal impact on the enantioselectivity of the transformation, as was observed with allene diboration.

Table 3.3. TADDOL-Derived Phosphoramidite Ligand Study with Modified Ketals for Diene Diboration

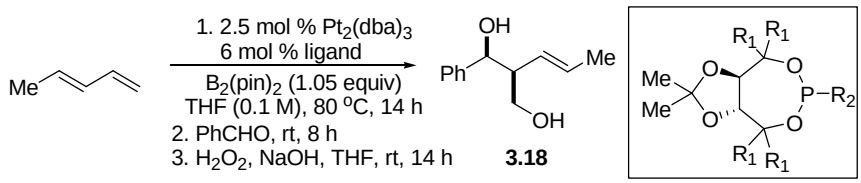


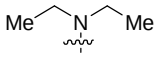
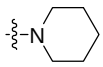
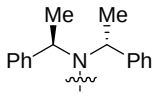
entry	ligand	R_1	1,4:1,2[a]	% yield (% ee)[b]
1	**(*R,R*)-3.23**	Me	1:0.32	49 (49)
2	**(*R,R*)-3.24**	H	1:0.67	35 (38)
3	**(*R,R*)-3.25**	$(CH_2)_5$	1:1	28 (10)

[a] Ratio of 1,4- to 1,2-bis(boronate)ester determined by the crude ^{1}H NMR ratio of the 1,4-diboration/allylation/oxidation product to the 1,2-diboration/allylation/oxidation product. [b] Isolated yield of the 1,3-diol after silica gel chromatography. Enantiomeric excess determined by chiral GLC analysis of the 1,3-diol protected as the dimethyl ketal.

The modification of both the amine moiety and the aryl groups of the highly tunable phosphoramidite ligand scaffold were investigated next. Diethylamine-derived phosphoramidite **(*R,R*)-3.26** afforded a 1:1 mixture of 1,4- to 1,2-bis(boronate)esters in poor yield and enantioselectivity. Phosphoramidites bearing pyrrolidine and piperidine moieties also failed to improve the yield and enantioselectivity for this transformation. As in the Pd-catalyzed diboration of allenes, phosphoramidite **(*R,R*)-3.29** failed to yield any of the desired 1,3-diol **3.18**, instead, only 1,5-diol **3.22** was obtained. All of the TADDOL-derived phosphoramidites with the amine moieties larger than dimethylamine provided reaction products consistent with the ligand-free Pt-catalyzed reaction pathway. TADDOL-derived phosphoramidites with 3,5-dialkyl-substituted aryl groups on the backbone also failed to increase the enantioselectivity for the 1,4-bis(boronate)ester (Table 3.4, entries 5-6).

Table 3.4. TADDOL-Derived Phosphoramidite Ligand Study for Diene Diboration



entry	ligand	R_1	R_2	1,4:1,2[a]	% yield (% ee)[b]
1	**(*R*,*R*)-3.26**	Ph		1:1	27 (-42)
2	**(*R*,*R*)-3.27**	Ph		0.87:1	19 (44)
3	**(*R*,*R*)-3.28**	Ph		0.67:1	30 (25)
4	**(*R*,*R*)-3.29**	Ph		0:1	0
5	**(*R*,*R*)-3.30**	xylyl	NMe_2	1:0	69 (35)
6	**(*R*,*R*)-3.31**	3,5-^{t}Bu$_2$C$_6$H$_3$	NMe_2	1:0.4	30 (6)

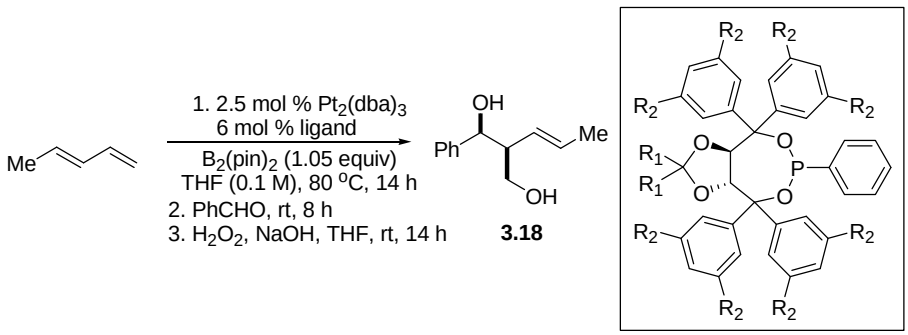
[a] Ratio of 1,4- to 1,2-bis(boronate)ester determined by the crude ^{1}H NMR ratio of the 1,4-diboration/allylation/oxidation product to the 1,2-diboration/allylation/oxidation product. [b] Isolated yield of the 1,3-diol after silica gel chromatography. Enantiomeric excess determined by chiral GLC analysis of the 1,3-diol protected as the dimethyl ketal.

After inferior enantioselectivities were obtained with TADDOL-derived phosphoramidites, we surveyed TADDOL-derived phosphonites, which were first prepared 15 years ago by Seebach and are used infrequently in asymmetric catalysis.[21] Parent phosphonite **(*R*,*R*)-3.32** provided modest but encouraging levels of asymmetric induction (62% ee) and reactivity (Table 3.5, entry 1). The TADDOL-derived

(21) (*a*) Seebach, D.; Hayakawa, M.; Sakaki, J. –I.; Schweizer, W. B. *Tetrahedron* **1993**, *49*, 1711. (*b*) Sakaki, J. –I.; Schweizer, W. B.; Seebach, D. *Helv. Chim. Acta* **1993**, *76*, 2654. (*c*) Haag, D.; Runsink, J.; Scharf, H. -D. *Organometallics* **1998**, *17*, 398. (*d*) Bee, C.; Han, S. B.; Hassan, A.; Iida, H.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 2746.

phosphonite **(*R*,*R*)-3.33**, with xylyl substituted aryl rings on the TADDOL backbone, provided a similar level of enantioselectivity when compared to the parent **(*R*,*R*)-3.32** ligand. However, higher regioselectivity for the formation of the 1,4-bis(boronate)ester **3.17** was observed with this ligand (entry 2). Diboration with ligand **(*R*,*R*)-3.34** provided 1,3-diol **3.18** in 20% ee. The reduction in the size of the ketal moiety, in conjunction with large sterically encumbered aryl groups on the TADDOL scaffold, also provided 1,3-diol **3.18** in low enantioselectivity (entry 5).

Table 3.5. TADDOL-Derived Phosphonite Ligand Study for Diene Diboration



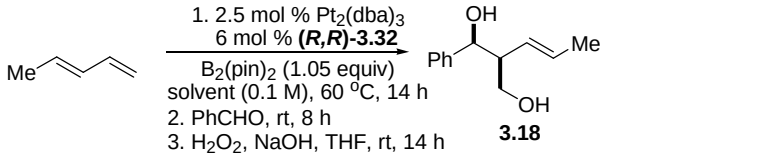
entry	ligand	R_1	R_2	1,4:1,2[a]	% yield (% ee)[b]
1	**(*R*,*R*)-3.32**	Me	H	1:0.18	58 (61)
2	**(*R*,*R*)-3.33**	Me	Me	1:0	40 (62)
3	**(*R*,*R*)-3.34**	Me	^{t}Bu	1:0.15	40 (20)
4	**(*R*,*R*)-3.35**	H	H	1:0.29	38 (51)
5	**(*R*,*R*)-3.36**	H	^{t}Bu	1:0.16	60 (25)

[a] Ratio of 1,4- to 1,2-bis(boronate)ester determined by the crude ^{1}H NMR ratio of the 1,4-diboration/allylation/oxidation product to the 1,2-diboration/allylation/oxidation product. [b] Isolated yield of the 1,3-diol after silica gel chromatography. Enantiomeric excess determined by chiral GLC analysis of the 1,3-diol protected as the dimethyl ketal.

The levels of asymmetric induction achieved thus far in the Pt-catalyzed diboration were in the low sixties. A brief solvent and temperature study was conducted next. When diboration with (*R*,*R*)-TADDOLPPh **(*R*,*R*)-3.32** was conducted in THF and

toluene, comparable enantiopurities of 1,3-diol **3.18** were obtained. However, preferential formation of the 1,4-bis(boronate)ester was achieved in toluene (Scheme 3.10).

Scheme 3.10. Solvent Study with (*R,R*)-TADDOLPPh **(*R,R*)-3.32**

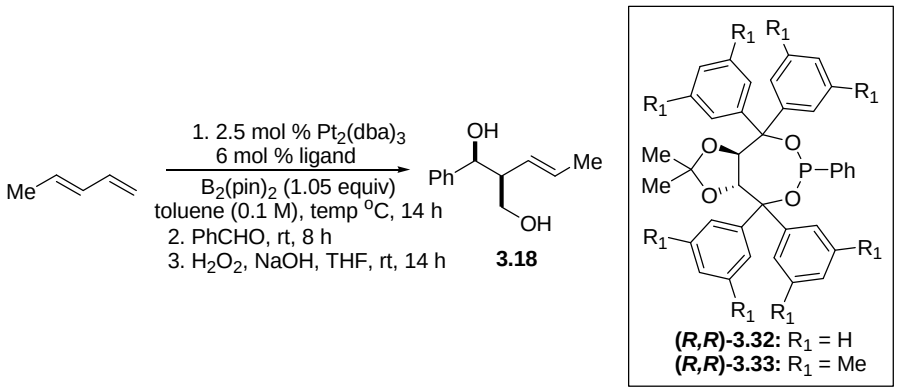


THF: 0.2:1(1,2:1,4) 58% y, 61% ee
toluene = 0.23:1 (1,2:1,4) 41% y, 62% ee

A temperature study for the asymmetric diboration was conducted in toluene with (*R,R*)-TADDOLPPh (ligand **(*R,R*)-3.32**) and (*R,R*)-xylylTADDOLPPh (ligand **(*R,R*)-3.33**) (Table 3.6). The isoinversion principle operates for the formation of 1,3-diol **3.18** with these ligands.[22] The enantioselectivities for the formation of 1,4-bis(boronate)ester **3.17** with ligands **(*R,R*)-3.32** and **(*R,R*)-3.33** were highest between 40 and 60 °C with lower enantioselectivities at 80 °C and room temperature. At room temperature with ligand **(*R,R*)-3.32**, 1,2-bis(boronate)ester **3.21** was formed. Diboration with ligand **(*R,R*)-3.33**, at all temperatures, favored the formation of 1,4-bis(boronate)ester **3.17**. Diene diboration with **(*R,R*)-3.33** at 60 °C delivered the optimal level of enantioselectivity observed thus far, 81% ee (Table 3.6, entry 6).

(22) Buschmann, H.; Scharf, H. -D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477.

Table 3.6. Temperature Study for Asymmetric Diene Diboration with $B_2(pin)_2$

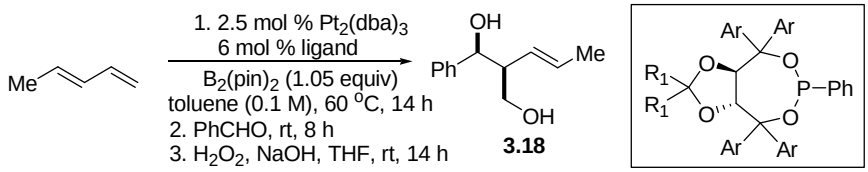


entry	ligand	temp (°C)	1,4:1,2[a]	% yield (% ee)[b]
1	**(*R,R*)-3.32**	80	1:0.23	41 (62)
2	**(*R,R*)-3.32**	60	1:0.43	75 (71)
3	**(*R,R*)-3.32**	40	1:0.08	55 (75)
4	**(*R,R*)-3.32**	rt	0.33:1	23 (59)
5	**(*R,R*)-3.33**	80	1:0	40 (62)
6	**(*R,R*)-3.33**	60	1:0	82 (81)
7	**(*R,R*)-3.33**	40	1:0	64 (78)
8	**(*R,R*)-3.33**	rt	trace	trace

[a] Ratio of 1,4- to 1,2-bis(boronate)ester determined by the crude ^{1}H NMR ratio of the 1,4-diboration/allylation/oxidation product to the 1,2-diboration/allylation/oxidation product. [b] Isolated yield of the 1,3-diol after silica gel chromatography. Enantiomeric excess determined by chiral GLC analysis of the 1,3-diol protected as the dimethyl ketal.

Several more TADDOL-derived phosphonites were prepared and surveyed in the diboration of *trans*-piperylene at 60 °C in toluene (Table 3.7). All modifications of the aryl group on the TADDOL backbone led to diminished enantioselectivities for the formation of *syn*-1,3-diol **3.18** (entries 3-6). Dioxalane substitution on the TADDOL scaffold delivered phosphonites which failed to increase the enantioselectivity of this transformation (Table 3.7, entry 7). 3,5-Dialkyl substitution on the aryl rings of the TADDOL scaffold, with the formaldehyde dioxalane, did not furnish 1,3-diol **3.18** with increased enantioselectivity (entries 8-9).

Table 3.7. TADDOL-Derived Phosphonite Ligand Survey for Diene Diboration at 60 °C

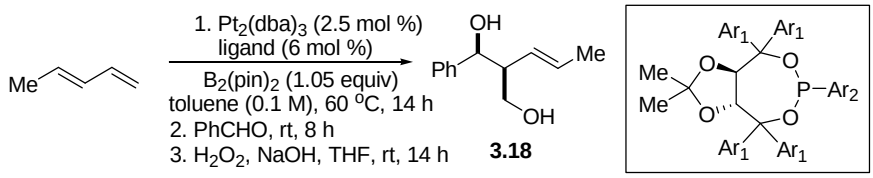


entry	ligand	R_1	Ar	1,4:1,2[a]	% yield (% ee)[b]
1	**(*R,R*)-3.32**	Me	Ph	1:0.43	75 (71)
2	**(*R,R*)-3.33**	Me	3,5-$Me_2C_6H_3$	1:0	82 (81)
3	**(*R,R*)-3.37**	Me	3,5-$Et_2C_6H_3$	1:0.06	69 (53)
4	**(*R,R*)-3.38**	Me	3,5-$^t Bu_2C_6H_3$	1:0.29	53 (32)
5	**(*R,R*)-3.39**	Me	1-naphthyl	1:0.38	39 (56)
6	**(*R,R*)-3.40**	Me	2-naphthyl	1:0.20	63 (-71)[c]
7	**(*R,R*)-3.35**	H	Ph	1:0.12	55 (80)
8	**(*R,R*)-3.41**	H	3,5-$Me_2C_6H_3$	1:0.54	65 (68)
9	**(*R,R*)-3.36**	H	3,5-$^t Bu_2C_6H_3$	1:0.29	53 (32)
10	**(*R,R*)-3.42**	Et	Ph	1:0.55	33 (65)

[a] Ratio of 1,4- to 1,2-bis(boronate)ester determined by the crude ^{1}H NMR ratio of the 1,4-diboration/allylation/oxidation product to the 1,2-diboration/allylation/oxidation product. [b] Isolated yield of the 1,3-diol after silica gel chromatography. Enantiomeric excess determined by chiral GLC analysis of the 1,3-diol protected as the dimethyl ketal. [c] (*S,S*)-2-naphthyl-TADDOL was employed, delivering the opposite enantiomer of **3.18**.

In order to further probe the TADDOL-derived phosphonite ligand structure for the diene diboration reaction, phosphonites with different aryl groups attached to phosphorus were examined (Table 3.8). All of the ligands that were synthesized and investigated in the diboration reaction were inferior to (*R,R*)-xylylTADDOLPPh (ligand **(*R,R*)-3.33**). Increasing the size of the aryl group bound to phosphorus had a negative impact on the enantioselectivity for this transformation, as illustrated with ligands **(*R,R*)-3.45** and **(*R,R*)-3.47**.

Table 3.8. Aryl-Phosphorus Derivatives of TADDOL-Derived Phosphonite Ligand Scaffold

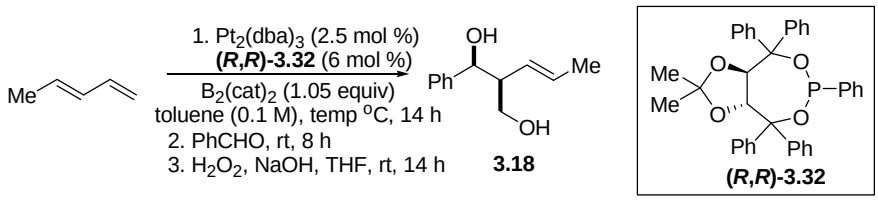


entry	ligand	Ar_1	Ar_2	1,4:1,2[a]	% yield (% ee)[b]
1	**(*R*,*R*)-3.43**	Ph	3,5-$Me_2C_6H_3$	1:0.26	82 (70)
2	**(*R*,*R*)-3.44**	3,5-$Me_2C_6H_4$	3,5-$Me_2C_6H_3$	1:0.19	49 (84)
3	**(*R*,*R*)-3.45**	Ph	*o*-MeC_6H_4	1:1.03	44 (16)
4	**(*R*,*R*)-3.46**	Ph	2-naphthyl	1:0	73 (62)
5	**(*R*,*R*)-3.47**	Ph	*p*-$OMeC_6H_4$	1:1	28 (65)

[a] Ratio of 1,4- to 1,2-bis(boronate)ester determined by the crude ^{1}H NMR ratio of the 1,4-diboration/allylation/oxidation product to the 1,2-diboration/allylation/oxidation product. [b]Isolated yield of the 1,3-diol after silica gel chromatography. Enantiomeric excess determined by chiral GLC analysis of the 1,3-diol protected as the dimethyl ketal.

Different diboron reagents were also investigated in an attempt to increase the enantioselectivities of diene diboration. Bis(catecholato)diboron was the only diboron reagent to furnish reactivity and enantioselectivity in the diboration of *trans*-piperylene. The isoinversion principle is also operative with $B_2(cat)_2$.[22] The highest level of enantioselectivity that was achieved with $B_2(cat)_2$ was 36% ee (entry 2).

Table 3.9. Temperature Study for Diene Diboration with $B_2(cat)_2$

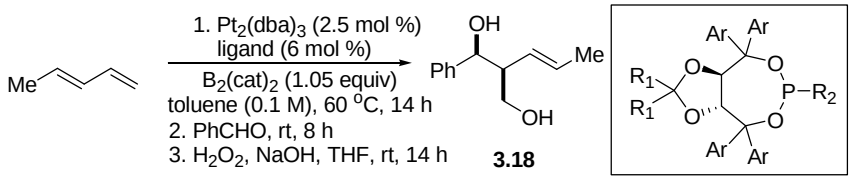


entry	temp (°C)	1,4:1,2[a]	% yield (% ee)[b]
1	80	1:0	59 (23)
2	60	1:0	70 (36)
3	rt	1:0	69 (25)

[a] Ratio of 1,4- to 1,2-bis(boronate)ester determined by the crude ^{1}H NMR ratio of the 1,4-diboration/allylation/oxidation product to the 1,2-diboration/allylation/oxidation product. [b] Isolated yield of the 1,3-diol after silica gel chromatography. Enantiomeric excess determined by chiral GLC analysis of the 1,3-diol protected as the dimethyl ketal.

A handful of TADDOL-derived phosphoramidites and phosphonites were surveyed with $B_2(cat)_2$ in the diboration reaction (Table 3.10). Predominant selectivity for the 1,4-diboration product occurred with $B_2(cat)_2$; unfortunately, the enantioselectivity for the reaction never rose above 60% ee.

Table 3.10. Diboration with $B_2(cat)_2$ Catalyzed by Various TADDOL-Derived Ligands

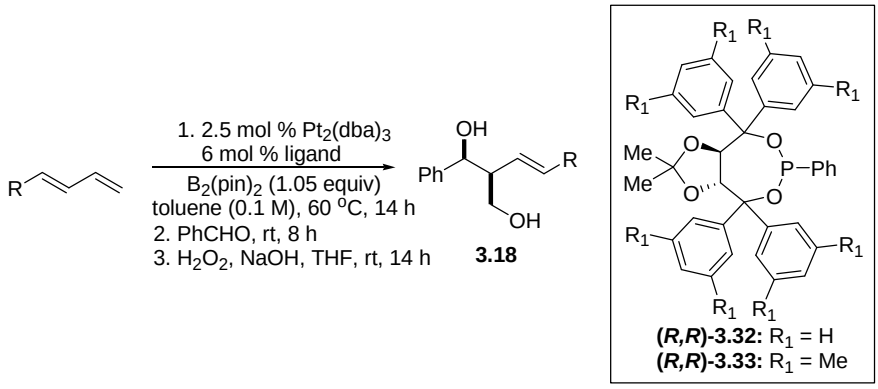


ligand	R_1	Ar	R_2	1,4:1,2[a]	% yield (% ee)[b]
(*R*,*R*)-3.23	Me	Ph	NMe_2	1:0	41 (55)
(*R*,*R*)-3.27	Me	Ph	$N(CH_2)_4$	1:0	37 (60)
(*R*,*R*)-3.33	Me	3,5-$Me_2C_6H_3$	Ph	1:0	37 (42)
(*R*,*R*)-3.36	H	3,5-^{t}Bu$_2$C$_6$H$_3$	Ph	1:0	41 (22)

[a] Ratio of 1,4- to 1,2-bis(boronate)ester determined by the crude ^{1}H NMR ratio of the 1,4-diboration/allylation/oxidation product to the 1,2-diboration/allylation/oxidation product. [b] Isolated yield of the 1,3-diol after silica gel chromatography. Enantiomeric excess determined by chiral GLC analysis of the 1,3-diol protected as the dimethyl ketal.

3.3.3. Substrate Scope. The highest level of asymmetric induction for the diboration of *trans*-piperylene achieved thus far was 81% ee. The substrate scope for the tandem-diboration/allylation/oxidation reaction sequence was then investigated. This reaction cascade works well for aliphatic dienes (up to 91% ee), but the desired 1,3-diols, arising from aldehyde allylation, were formed in low yields (Table 3.11).

Table 3.11. Substrate Scope for Diene Diboration/Allylation/Oxidation



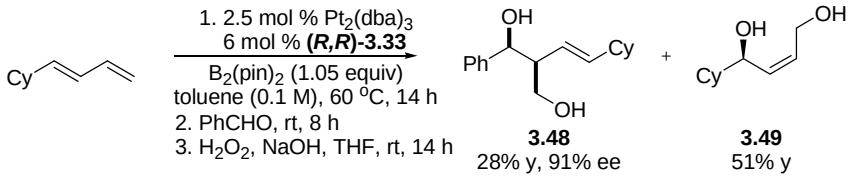
entry	ligand	R	% yield (% ee)[a]
1	**(*R,R*)-3.32**	Et	54 (73)
2	**(*R,R*)-3.33**	Et	60 (82)
3	**(*R,R*)-3.33**	*n*-Hexyl	46 (82)
4	**(*R,R*)-3.33**	Cy	28 (91)

[a] Isolated yield of the 1,3-diol after silica gel chromatography. Enantiomeric excess determined by chiral GLC analysis of the 1,3-diol protected as the dimethyl ketal.

After the crude reaction mixture from the diboration/allylation/oxidation of (*E*)-1-cyclohexyl-1,3-butadiene was purified, a side product (**3.49**) was isolated (Scheme 3.11). Apparently, the aldehyde allylation with the 1,4-bis(boronate)ester resulting from the diboration of (*E*)-1-cyclohexyl-1,3-butadiene was incomplete, direct oxidation of the 1,4-bis(boronate)ester occurred to deliver the 1,4-dihydroxylated product **3.49**. While, there

are a few examples in the literature for the 1,4-dihydroxylation of dienes,[23] only one has been rendered enantioselective, delivering the 1,4-dihydroxylated product in 54% ee.[24]

Scheme 3.11. Diboration of (*E*)-1-Cyclohexyl-1,3-butadiene

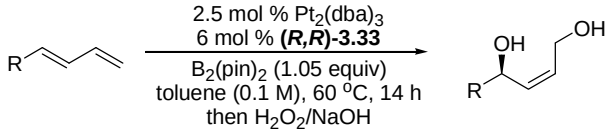


3.3.4. Development of the 1,4-Dihydroxylation of 1,3-Dienes. The development of the asymmetric 1,4-dihydroxylation of dienes would allow access to a challenging class of targets. Aside from the Lindlar reduction of an alkyne, there are few examples in the literature for the preparation of a *cis*-1,4-diol.[25] Along these lines, several prochiral monosubstituted dienes were prepared and investigated in the asymmetric 1,4-dihydroxylation reaction (Table 3.12). Diboration of primary aliphatic and aromatic dienes afforded 1,4-diols in 83-84% ee (entries 2-4). Secondary and tertiary aliphatic dienes were very effective in the diboration, and the desired reaction products were obtained in 90 and 92% ee (entries 1, 5). The 1,4-diol resulting from the diboration of (*E*)-1-cyclohexyl-1,3-butadiene was isolated in 90% ee; this observation proved an earlier

(23) Matsumoto, M.; Dobashi, S.; Kuroda, K.; Kondo, K. *Tetrahedron* **1985**, *41*, 2147.
(24) (*a*) Bäckvall, J. –E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619. (*b*) Bäckvall, J. –E.; Vågberg, J. O. *J. Org. Chem.* **1988**, *53*, 5695. (c) Itami, K.; Palmgren, A.; Thorarensen, A.; Bäckvall, J. -E. *J. Org. Chem.* **1998**, *63*, 6466.
(25) (*a*) Bloch, R.; Gilbert, L. *Tetrahedron Lett.* **1987**, *28*, 423. (*b*) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015. (*c*) Whitehead, A.; McReynolds, M. D.; Moore, J. D.; Hanson, P. R. *Org. Lett.* **2005**, *7*, 3375. (*d*) Jernelius, J. A.; Schrock, R. R.; Hoveyda, A. H. *Tetrahedron* **2004**, *60*, 7345.

assumption that the conservation of chirality in the allylation reaction of the intermediate 1,4-bis(boronate)esters was high.

Table 3.12. Expansion of the Substrate Scope for 1,4-Dihydroxylation of 1,3-Dienes

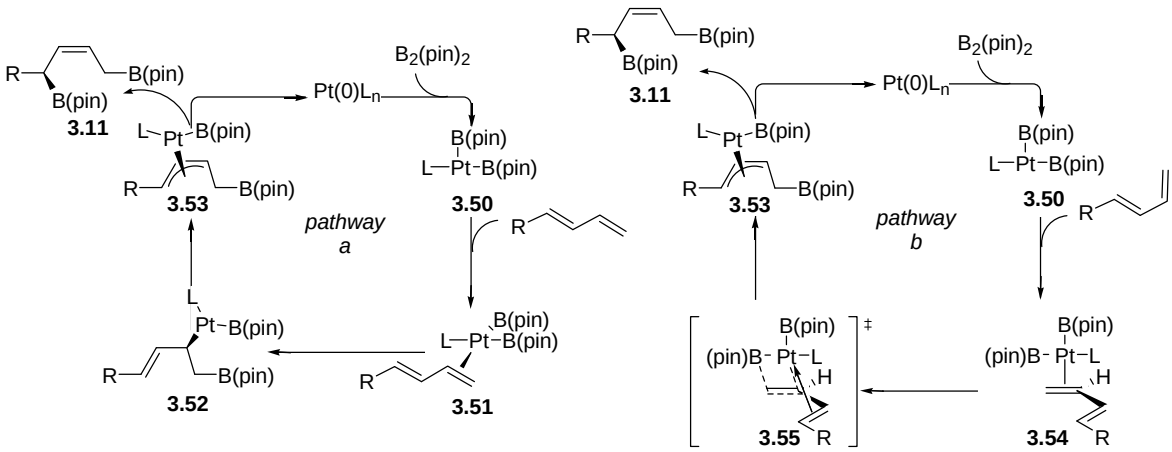


entry	R	% yield (% ee)[a]
1	Cy	82 (90)
2	*n*-Hexyl	84 (83)
3	$PhCH_2CH_2$	81 (84)
4	Ph	80 (84)
5	*t*-Bu	30 (92)

[a] Isolated yield of the 1,4-diol after silica gel chromatography. Enantiomeric excess was determined by chiral GLC after ozonlysis of the 1,4-diol and subsequent protection as the dimethyl ketal.

3.3.5. Mechanistic Experiments. There are two possible mechanisms for the asymmetric diene diboration (Scheme 3.12, pathways a and b). Both mechanisms center on oxidative addition of $B_2(pin)_2$ to platinum; however, they differ in the mode of diene insertion. The first mechanism (pathway a) involves coordination of the platinum-bis(boryl) **3.50** to the terminal bond of the diene (**3.51**), followed by insertion to deliver the η^1-allyl intermediate **3.52**. Reductive elimination from **3.52** delivers the 1,2-bis(boronate)ester; however, π-allyl isomerization to **3.53** followed by reductive elimination, would deliver 1,4-bis(boronate)ester **3.11**.

Scheme 3.12. Potential Mechanisms for Diene Diboration



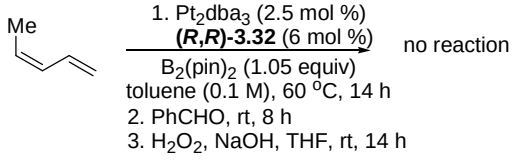
The second mechanism is closely tied to the mechanism for the enantioselective palladium-catalyzed diboration of allenes (Scheme 3.12, pathway b). Bis(boryl) **3.50** would coordinate to the π-system of the diene when the diene (**3.54**). Analogous to the mechanism for allene diboration, π-allyl formation occurs concomitantly with carbon-boron bond formation (**3.55**). Reductive elimination from π-allyl intermediate **3.53** affords the desired 1,4-bis(boronate)ester **3.11**. A requirement for this mechanism is that the diene adopt an *s-cis* conformation.

In order to differentiate between these mechanistic pathways, the platinum-catalyzed diboration of *cis*-piperylene was conducted (Scheme 3.13). *Cis*-piperylene is energetically less likely to adopt the *s-cis* diene conformation required for diboration through the mechanism in pathway b (Scheme 3.12).[26] If insertion of the terminal alkenes of piperylene into the B-Pt bond of bis(boryl) **3.50** occurs without association of the adjacent alkene, then there is no requirement for the diene to adopt the *s-cis*

(26) 3.51 kcal/mol is the calculated energy required for *cis*-piperylene to adopt the *s-cis* conformation. Dodzuik, H. *J. Mol. Struct.* **1974**, *20*, 317.

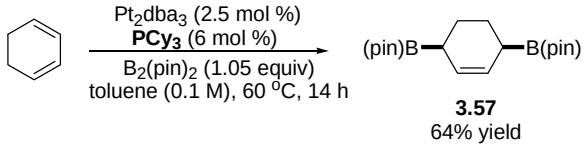
conformation (Scheme 3.12, pathway a). In fact, when *cis*-piperylene is subjected to the optimized reaction conditions with (*R,R*)-TADDOLPPh (ligand **3.32**), no diboration occurred: the 1,3- and 1,5-diols resulting from the formation of 1,4-bis(boronate)ester **3.17** and 1,2-bis(boronate)ester **3.21**, respectively, were not observed in the crude ^{1}H NMR. Diols resulting from diboration were not obtained when tricyclohexylphosphine was employed as the ligand on platinum. Based on these experiments, the most likely mechanistic pathway is the one proposed in Scheme 3.12, pathway b.

Scheme 3.13. Diboration of *cis*-Piperylene



Further evidence to support the requirement that the substrate adopt the *s-cis* conformation, comes from the diboration of 1,3-cyclohexadiene (Scheme 3.14). In fact, diboration of this substrate proceeded with tricyclohexylphosphine, as the ligand for platinum, to provide 1,4-bis(boronate)ester **3.57** in 64% yield. While these mechanistic experiments are preliminary, both support the requirement for the diene to be in the *s-cis* conformation and that carbon-bond formation may occur concurrently with π-allyl formation, analogous to the mechanism for allene diboration.

Scheme 3.14. Diboration of 1,3-Cyclohexadiene



3.57
64% yield

3.4. Conclusion

The asymmetric platinum-catalyzed diboration of prochiral monosubstituted dienes affords 1,4-bis(boronate)esters in high enantioselectivities. 1,4-Bis(boronate)esters obtained from diene diboration will allylate aldehydes with near perfect chirality transfer. Direct oxidation of the 1,4-bis(boronate)ester delivered an optically enriched 1,4-dihydroxylated product which allowed access to a challenging class of targets in a single reaction vessel.

3.5. Experimentals

3.5.1. General Procedure. ^{1}H NMR spectra were recorded on Varian Unity Inova 500 MHz and Varian Gemini 400 MHz spectrometers. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentad, br = broad, m = multiplet), coupling constants (Hz) and assignment. $^{13}C\{^{1}H\}$NMR spectra were recorded on Varian Unity Inova 500 MHz (125 MHz) and Varian Gemini 400 MHz (100 MHz) spectrometers. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.16 ppm). $^{31}P\{^{1}H\}$NMR (121 MHz) were recorded on a Varian Unity Inova 300 spectrometer. Chemical shifts are reported for ^{31}P NMR spectra using phosphoric acid as an external standard. Infrared (IR) spectra were recorded on a Bruker α-P Spectrometer. Frequencies are reported in wavenumbers (cm^{-1}) as follows: strong (s), broad (br), medium (m), and weak (w). High-resolution mass spectrometry (ESI) was performed at Boston College, Chestnut Hill, MA.

Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 230 x 450 Mesh) purchased from Silicycle. Thin layer chromatography was performed on 25 μm silica gel glass backed plates from Silicycle. Visualization was performed using ultraviolet light, phosphomolybdic acid (PMA), and potassium permanganate ($KMnO_4$).

Analytical gas-liquid chromatography (GLC) was performed on a Hewlett-Packard 6890 Series chromatograph equipped with a CTC Analysis Combi Pal autosampler by

Leap Technologies (Carrboro, North Carolina), a split mode capillary injection system, a flame ionization detector, and a Supleco β-Dex 120 column with helium as the carrier gas. Analytical chiral supercritical fluid chromatography (SFC) was performed on a Berger Instruments Supercritical Chromatograph equipped with an Alcott auto sampler and a Knauer UV detector.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Toluene, tetrahydrofuran, methylene chloride, and diethyl ether were purified using Pure Solv MD-4 solvent purification system, from Innovative Technology, Inc., by passing the solvent through two activated alumina columns after being purged with argon. Triethylamine was distilled from calcium hydride. Potassium tetrachloroplatinate(II) was purchased from Strem Chemicals, Inc. Bis(pinacolato)diboron was obtained from Allychem Co., Ltd. and recrystallized from pentanes prior to use. Dibenzylideneacetone was purchased from Oakwood Chemicals. *trans*-1,3-Hexadiene and *cis*-piperylene were purchased from TCI America. All other reagents were purchased from Aldrich and used without further purification.

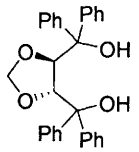
3.5.2. Preparation for $Pt_2(dba)_3$. Tris(dibenzylideneacetone)diplatinum was prepared using the literature procedure[27] with slight modification. To a 3-neck 500-mL round-bottomed flask equipped with a magnetic stir bar and reflux condenser was added dibenzylideneacetone (3.95 g, 16.8 mmol), tetrabutylammonium chloride (2.0 g, 7.2 mmol), and sodium acetate (3.55 g, 43.3 mmol). Salts were dissolved in methanol and

(27) Lewis, L. N.; Krafft, T. A.; Huffman, J. C. *Inorg Chem.* **1992**, *31*, 3555.

the solution was warmed to 70 °C and allowed to stir for 5 min. To a 50-mL pear-shaped flask was added potassium tetrachloroplatinate (1.00 g, 2.41 mmol). The potassium salt was dissolved in water (8 mL) with mild heating. The 3-neck round-bottomed flask was charged with the potassium tetrachloroplatinate solution and the reaction was allowed to stir at 70 °C for 3 h. After 3 h, the reaction was cooled to ambient temperature, transferred to a 500-mL round-bottomed flask and contentrated on the rotary evaporation to half the volume. The reaction mixture was filtered on a Büchner funnel; solids were washed with copious amounts of water and methanol until all yellow crystals were no longer visible. The platinum catalyst was placed under the high vacuum for 24 h to remove residual methanol and water, and tris(dibenzylideneacetone)diplatinum was obtained as a brown solid (1.71 g, 65% yield). Spectroscopic characterization of the platinum catalyst was in accord with spectra reported in the literature.[27]

3.5.3. General Procedure for the Synthesis of TADDOL-Derivatives. To an oven-dried 2-neck 500-mL round-bottomed flask equipped with a magnetic stir bar, addition funnel, and reflux condenser was added magnesium (6.52 g, 268.2 mmol). The apparatus was flame-dried and allowed to cool to room temperature. A crystal of iodine was added to the 500-mL flask. Bromobenzene (26.5 mL, 252.4 mmol) was added to the addition funnel and diluted with tetrahydrofuran (252 mL). The bromobenzene solution was added dropwise over 1 h, at room temperature, to the magnesium. After the entire bromobenzene solution was added to the round-bottomed flask, the reaction mixture was refluxed for 1 h, or until the magnesium was completely consumed. The reaction mixture was allowed to cool to ambient temperature and was then cooled to 0 °C (ice/water bath).

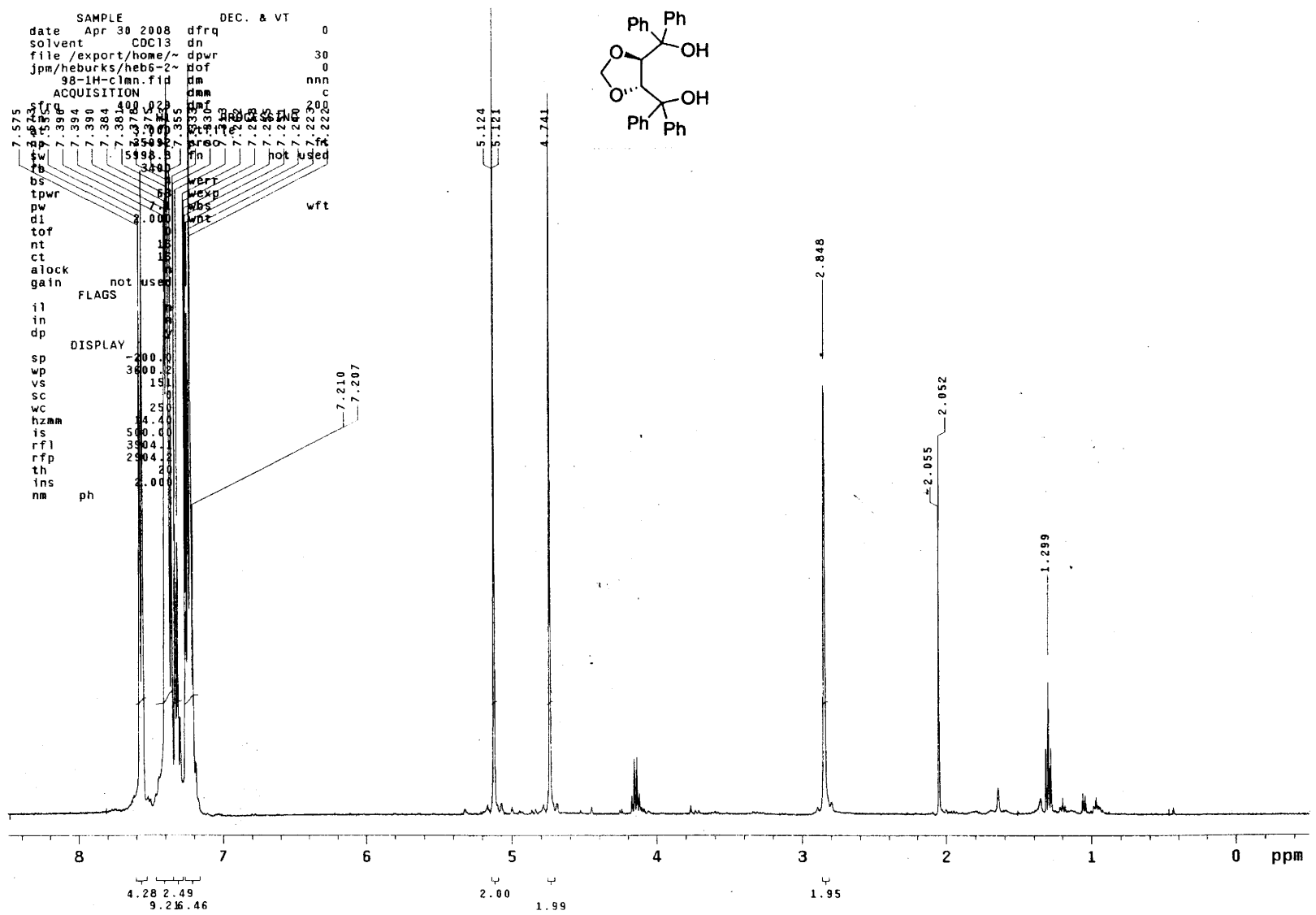
The addition funnel was charged with the dimethyl ester of (4*R*,5*R*)-1,3-dioxolane-4,5-dicarboxylic acid[28] (6.00 g, 31.55 mmol) and THF (63 mL). The reaction mixture was charged with a solution of the dimethyl ester of (4*R*,5*R*)-1,3-dioxolane-4,5-dicarboxylic acid over the course of 1 h. After the complete addition of the tartrate derivative, the reaction mixture was heated at 80 °C and allowed to stir overnight at 80 °C. At this time, the reaction was cooled to 0 °C and charged with a saturated ammonium chloride solution. The solid/liquid mixture was diluted with water and ethyl acetate and transferred to a separatory funnel. The organic and aqueous layers were separated; the aqueous layer was washed three times with ethyl acetate. The organic extracts were combined and washed with brine. The organic layer was dried (Na_2SO_4), filtered through cotton, and volatiles were removed on the rotary evaporation to afford a yellow solid. The solid was purified by column chromatography to afford ((4*R*,5*R*)-1,3-dioxolane-4,5-diyl)bis(diphenylmethanol) as a white solid (10.3 g, 75% yield).



((4*R*,5*R*)-1,3-Dioxolane-4,5-diyl)bis(diphenylmethanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.84 (2H, br s, O**H** x 2), 4.74 (2H, s, C**H**O), 5.12 (2H, s, CH_2O), 7.20-7.26 (6H, m, Ar**H**), 7.31-7.33 (1H, m, Ar**H**), 7.35-7.39 (9H, m, Ar**H**), 7.55-7.57 (4H, m, Ar**H**). ^{13}C NMR (100 MHz, $CDCl_3$) δ 78.8, 80.8, 97.2, 126.8, 127.2, 127.3, 127.6, 127.9, 128.2, 143.8, 144.7. IR (neat): 3379 (w), 3056 (w), 3024 (w), 2882 (w), 1446 (m), 694 (s) cm^{-1}. HRMS-(ESI+): for $C_{29}H_{26}NaO_4$ calc'd: 461.1729 $(M+Na)^+$, observed: 461.1730 $(M+Na)^+$. The unpurified reaction mixture was purified on silica gel

(28) Gerard, B.; Sangji, S.; O'Leary, D. J.; Porco, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 7754.

with 15% ethyl acetate/hexanes as the eluant to afford a white solid in 75% yield (10.3 g). $R_f = 0.25$ (10% ethyl acetate, stain in PMA).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7.207
5.124
5.121
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2.848
2.055
2.052
1.299
Ph
OH
O
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7
6
5
4
3
2
1
0
ppm
4.28
2.49
9.21
6.46
2.00
1.99
1.95

heb6-298-13C-clmn

exp3 std13c

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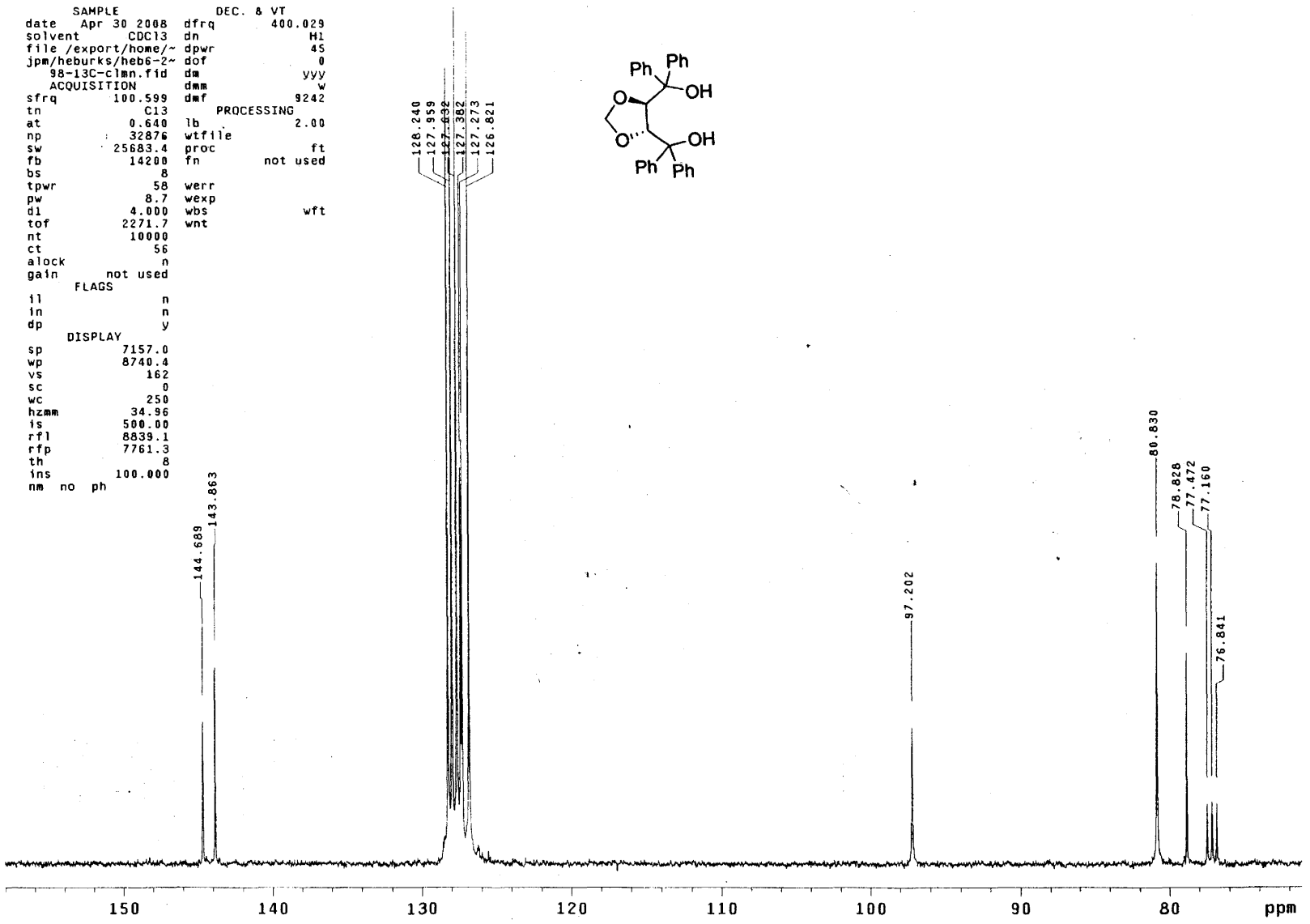
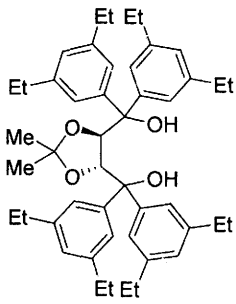
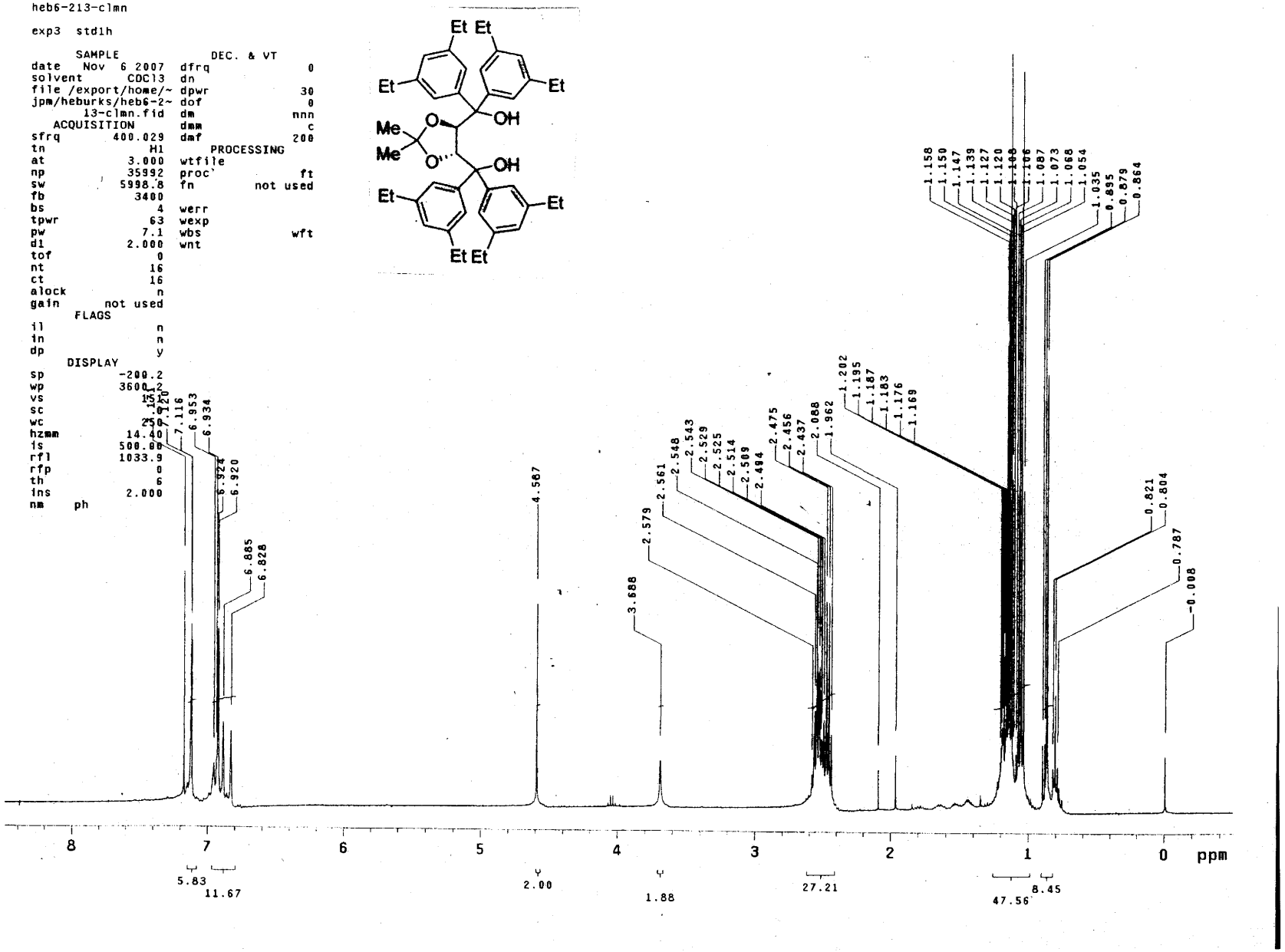




((4*R*,5*R*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(bis(3,5-diethylphenyl)methanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (6H, s, $(CH_3)_2C$), 1.05 (12H, t, J = 7.6 Hz, CH_3CH_2Ar), 1.13 (12H, t, J = 7.6 Hz, CH_3CH_2Ar), 2.47 (8H, q, J = 7.6 Hz, CH_3CH_2Ar), 2.53 (8H, q, J = 7.6 Hz, CH_3CH_2Ar), 3.68 (2H, br s, O**H** x 2), 4.58 (2H, s, C**H**O), 6.82 (1H, s, Ar**H**), 6.88 (2H, s, Ar**H**), 6.92-6.93 (4H, m, Ar**H**), 6.95 (1H, m, Ar**H**), 7.11-7.12 (4H, m, Ar**H**). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.6, 16.0, 27.2, 29.0, 29.2, 78.4, 81.1, 109.4, 124.7, 125.9, 126.2, 126.6, 142.7, 142.8, 143.7, 146.1. IR (neat): 3523 (w), 3322 (m), 2962 (s), 2930 (s), 2870 (s), 1598 (s), 1457 (s), 1368 (s), 1318 (s), 1169 (s), 1064 (s), 870 (s) cm^{-1}. HRMS-(ESI+): for $C_{47}H_{62}NaO_4$ calc'd: 713.4546 $(M+Na)^+$, observed: 713.4523 $(M+Na)^+$. The unpurified reaction mixture was purified on silica gel with 10% ethyl acetate/hexanes as the eluant to afford a brown-orange solid in 58% yield (1.731 g). R_f = 0.50 (10% ethyl acetate, stain in PMA).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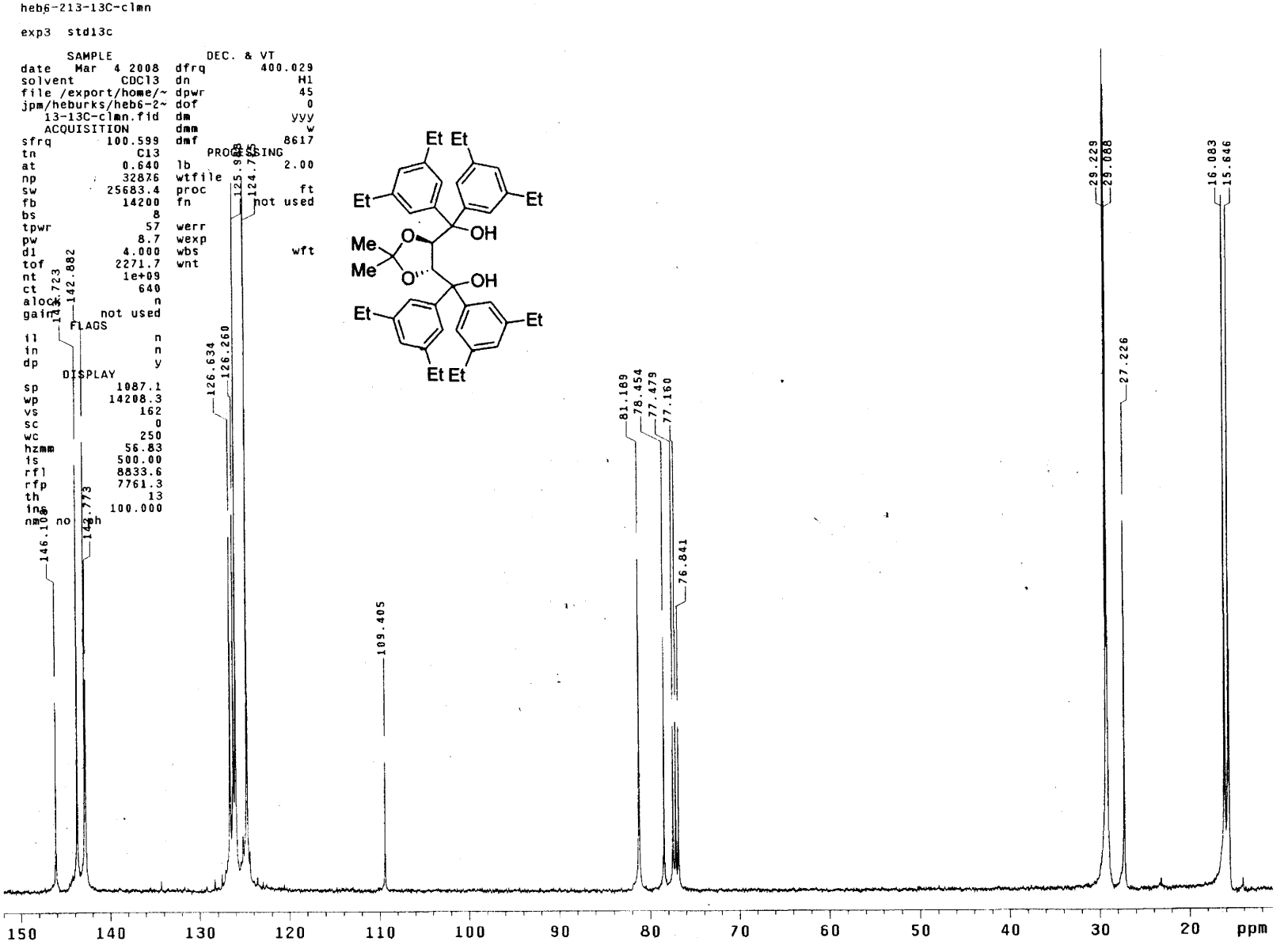
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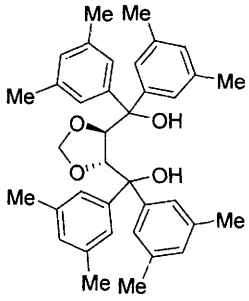

((4*R*,5*R*)-1,3-Dioxolane-4,5-diyl)bis(bis(3,5-dimethylphenyl)methanol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.18 (12H, s, C**H**$_3$Ar), 2.30 (12H, s, C**H**$_3$Ar), 2.49 (2H, s, O**H** x 2), 4.86 (2H, s, C**H**O), 5.03 (2H, s, C**H**$_2$O), 6.73 (2H, s, Ar**H**), 6.86 (4H, s, Ar**H**), 6.88 (2H, s, Ar**H**), 7.11 (4H, s, Ar**H**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.70, 21.73, 79.2, 81.0, 97.6, 124.3, 125.2, 129.0, 137.2, 137.0, 144.2, 144.5. IR (neat): 3537 (m), 3005 (m), 2913 (m), 1600 (s), 1470 (m), 1452 (m), 1441 (m), 1148 (s), 1099 (s), 1030 (s), 849 (s) cm^{-1}. HRMS-(ESI+): for $C_{37}H_{42}NaO_4$ calc'd: 573.2981 $(M+Na)^+$, observed: 573.2949 $(M+Na)^+$. The unpurified reaction mixture was purified on silica gel with 10% ethyl acetate/hexanes as the eluant to afford white solid in 2.35 g (80%). R_f = 0.21 (10% ethyl acetate, stain in PMA).

heb6-204-1H-clmn

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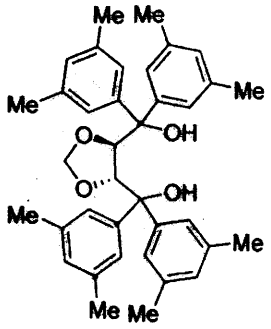
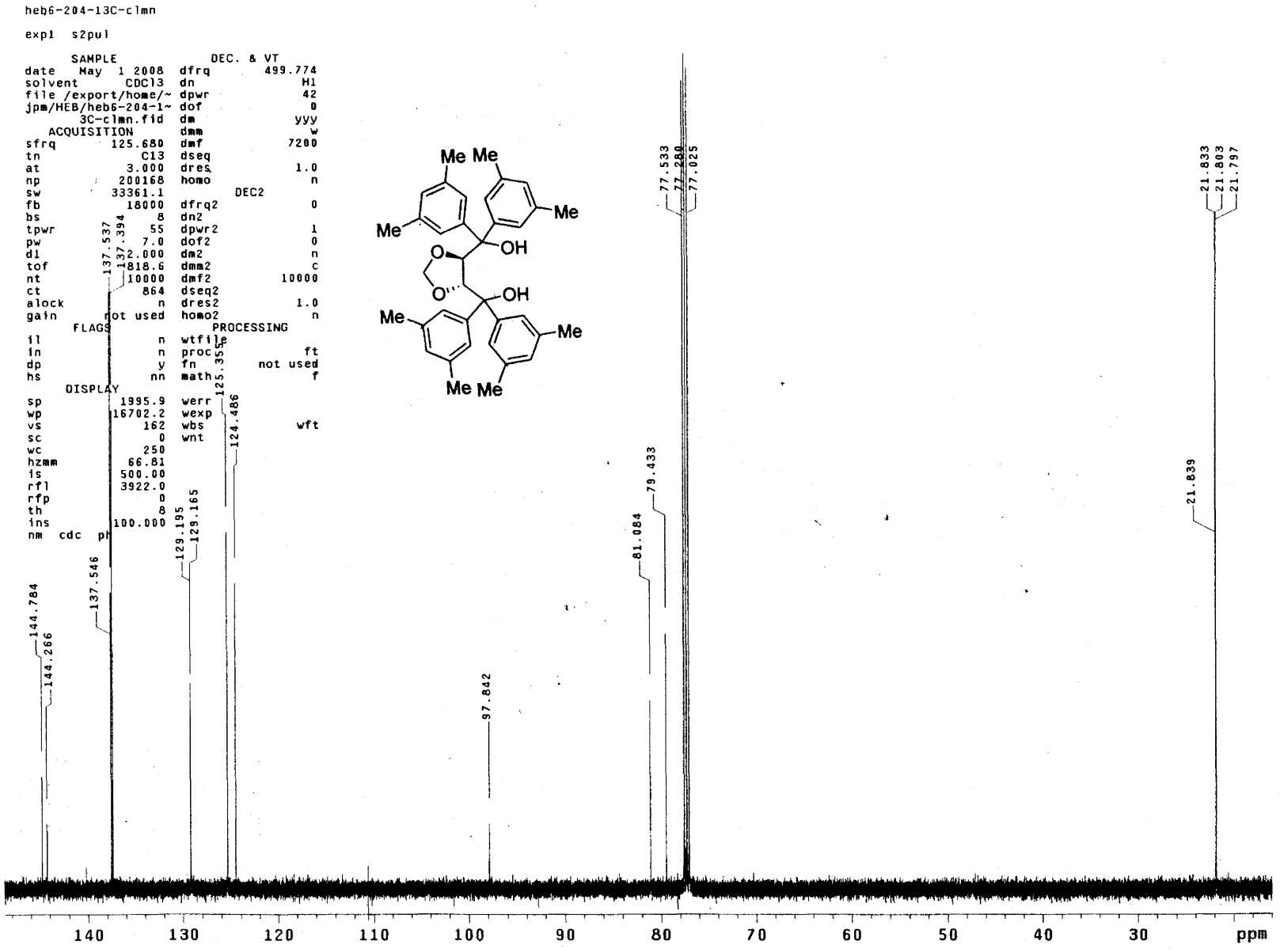
nm	ph		

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date May 1 2008
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dres 1.0
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dpwr2 1
dof2 0
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dmm2 c
dmf2 10000
dseq2
dres2 1.0
homo2 n
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wbs wft
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OH
Me
Me
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125.355
124.486
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129.165
137.546
144.784
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97.842
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79.433
77.533
77.280
77.025
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50
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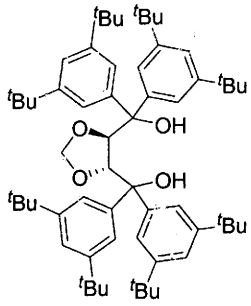
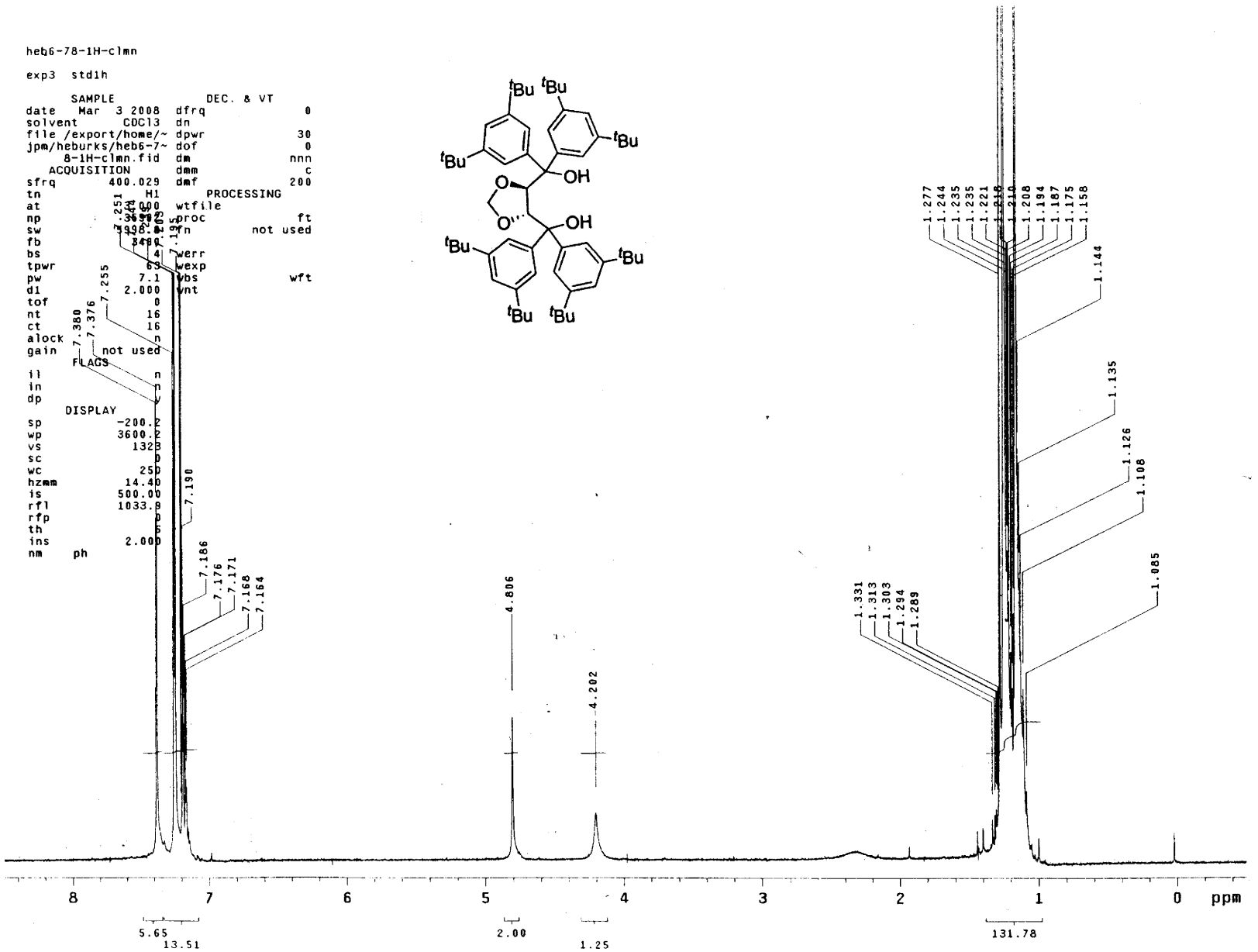
30
ppm



((4*R*,5*R*)-1,3-Dioxolane-4,5-diyl)bis(bis(3,5-di-*tert*-butylphenyl)methanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10-1.33 (72H, m, $(CH_3)_3C$), 4.20 (2H, s, CH_2O), 4.80 (2H, s, CHO x 2), 7.16 (1H, m, ArH), 7.17-7.18 (3H, m, ArH), 7.20-7.25 (3H, m, ArH), 7.37-7.38 (5H, m, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.5, 31.6, 31.7, 35.0, 78.7, 82.1, 96.1, 120.7, 121.0, 121.5, 122.1, 122.3, 122.4, 127.7, 142.1, 144.5, 149.7, 150.1. IR (neat): 3565 (m), 3545 (m), 2953 (s), 2903 (s), 2873 (s), 1596 (s), 1475 (s), 1361 (s), 1247 (s), 1171 (s), 948 (s) cm^{-1}. HRMS-(ESI+): for $C_{61}H_{90}NaO_4$ calc'd: 909.6737 $(M+Na)^+$, observed: 909.6684 $(M+Na)^+$. The unpurified reaction mixture was purified on silica gel with 5% ethyl acetate/hexanes as the eluant to afford a yellow solid in 71% yield (3.40 g). R_f = 0.65 (10% ethyl acetate, stain in PMA).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dp y
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rfp 0
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nm ph
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dpwr 30
dof 0
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dmm c
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werr
wexp
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1.313
1.303
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1.289
1.277
1.244
1.235
1.235
1.221
1.210
1.208
1.194
1.187
1.175
1.158
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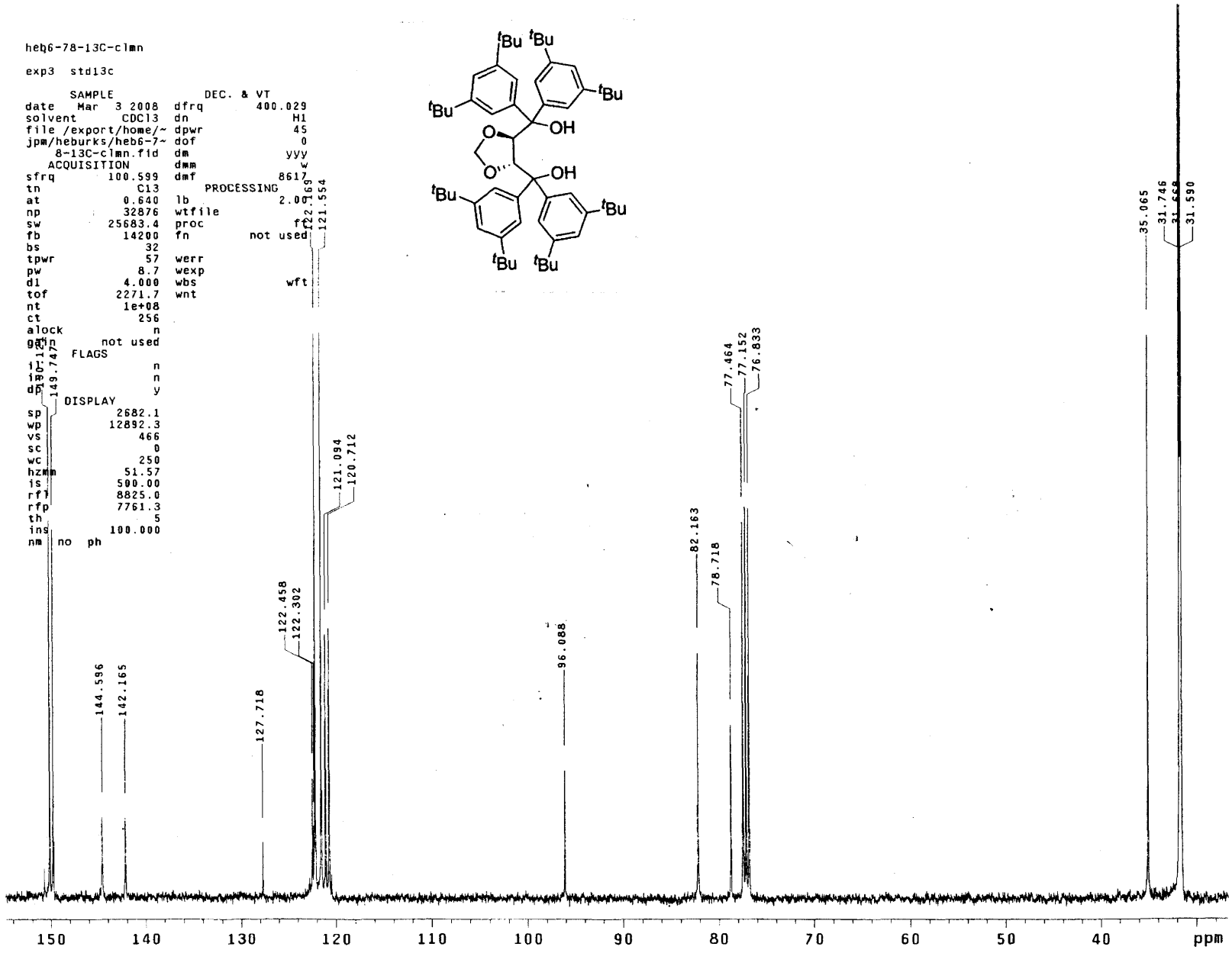
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121.554
121.094
120.712
96.088
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78.718
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77.152
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31.746
31.590
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140
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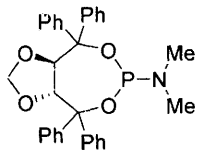
120
110
100
90
80
70
60
50
40
ppm

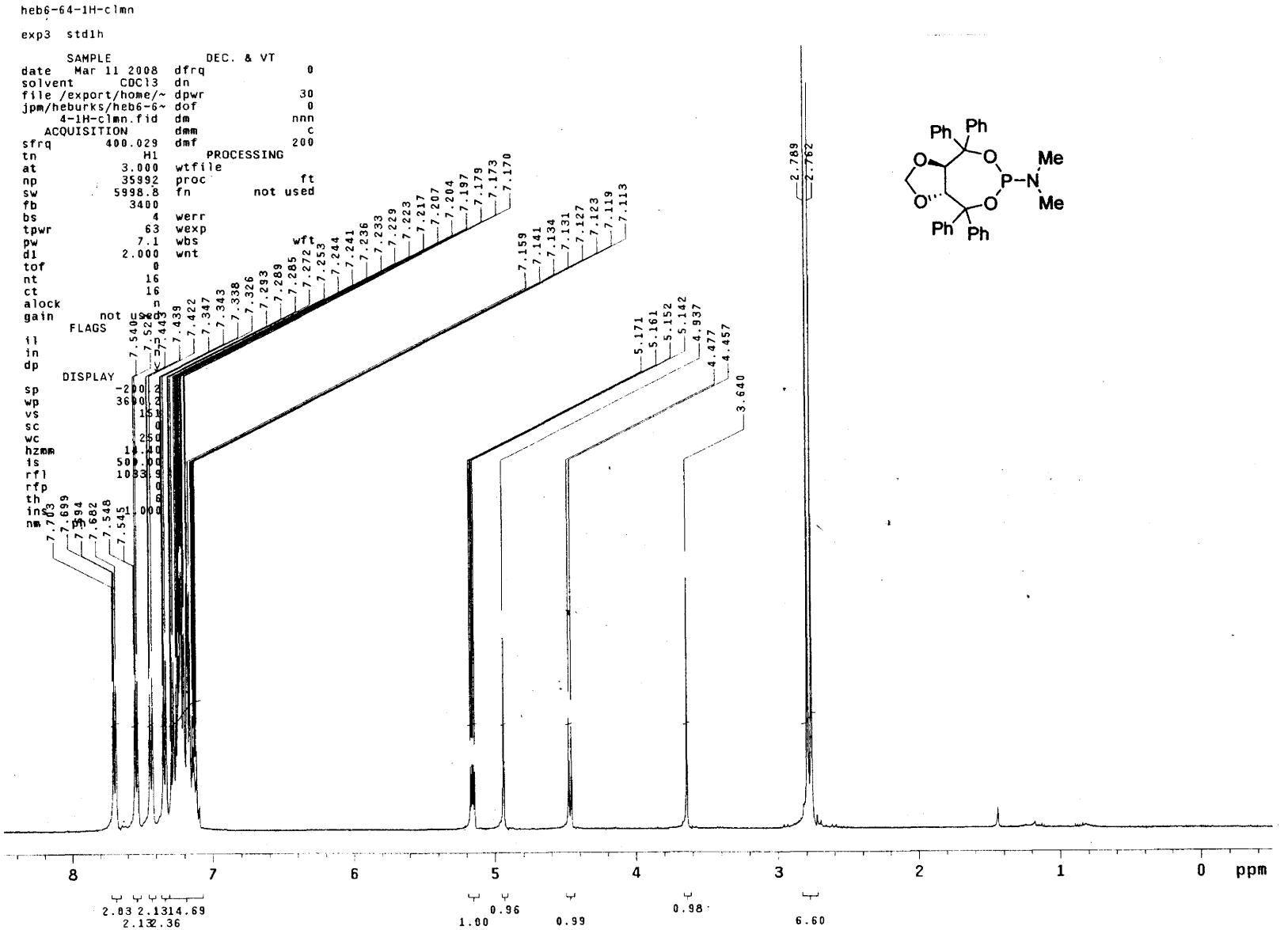
3.5.4. Ligand Synthesis.

3.5.4.1. General Procedure for (R,R)-TADDOL-Derived Phosphoramidite Ligands: All phosphoramidites were prepared according to the general procedure in Chapter 2 and spectral properties of the ligands are in accordance with the literature. Please see section 2.5.3.



(*R,R*)-3.24

(3a*R*,8a*R*)-*N,N*-Dimethyl-4,4,8,8-tetraphenyl-tetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-amine (*R,R*)-3.24. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.77 (6H, d, J_{HP} = 10.8 Hz, $(CH_3)_2N$), 3.64 (1H, s, OCH_AH_BO), 4.46 (1H, d, J = 8 Hz, CHO), 4.93 (1H, s, OCH_AH_BO), 5.16 (1H, dd, J = 7.6 Hz, J_{HP} = 4 Hz, CHO), 7.11-7.19 (12H, m, ArH), 7.32-7.34 (2H, m, ArH), 7.42-7.44 (2H, m, ArH), 7.52-7.54 (2H, m, ArH), 7.68-7.70 (2H, m, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.6 (d, $^{2}J_{CP}$ = 19.5 Hz), 80.4 (d, $^{2}J_{CP}$ = 7.1 Hz), 80.8, 81.2 (d, $^{3}J_{CP}$ = 24.2 Hz), 84.5 ($^{3}J_{CP}$ = 3.9 Hz), 95.8, 126.9, 127.0, 127.3, 127.53, 127.58, 127.6, 127.8, 127.9, 128.0, 128.2, 128.3, 140.7, 141.8, 145.6, 146.5. ^{31}P NMR (121 MHz, $CDCl_3$) δ 142.6. IR (neat): 2962 (m), 2929 (m), 2872 (m), 1599 (s), 1491 (s), 971 (s), 783 (s) cm^{-1}. HRMS-(ESI+): for $C_{31}H_{31}O_4NP$ calc'd: 512.1991 $(M+H)^+$, observed: 512.1985 $(M+H)^+$. The unpurified reaction mixture was purified on silica gel with 5% ethyl acetate/hexanes as the eluant to afford a white solid in 74% yield (527 mg). R_f = 0.55 (10% ethyl acetate, stain in PMA).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ct 16
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il
in
dp
DISPLAY
sp
wp
vs
sc
wc
hzmm
is
rfl
rfp
th
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dmm c
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wbs wft
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7.272
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7.233
7.229
7.223
7.217
7.207
7.204
7.197
7.179
7.173
7.170
7.159
7.141
7.134
7.131
7.127
7.123
7.119
7.113
5.171
5.161
5.152
5.142
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4.477
4.457
3.640
2.789
2.762
Ph
Ph
O
O
P–N
Me
Me
O
O
Ph
Ph
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5
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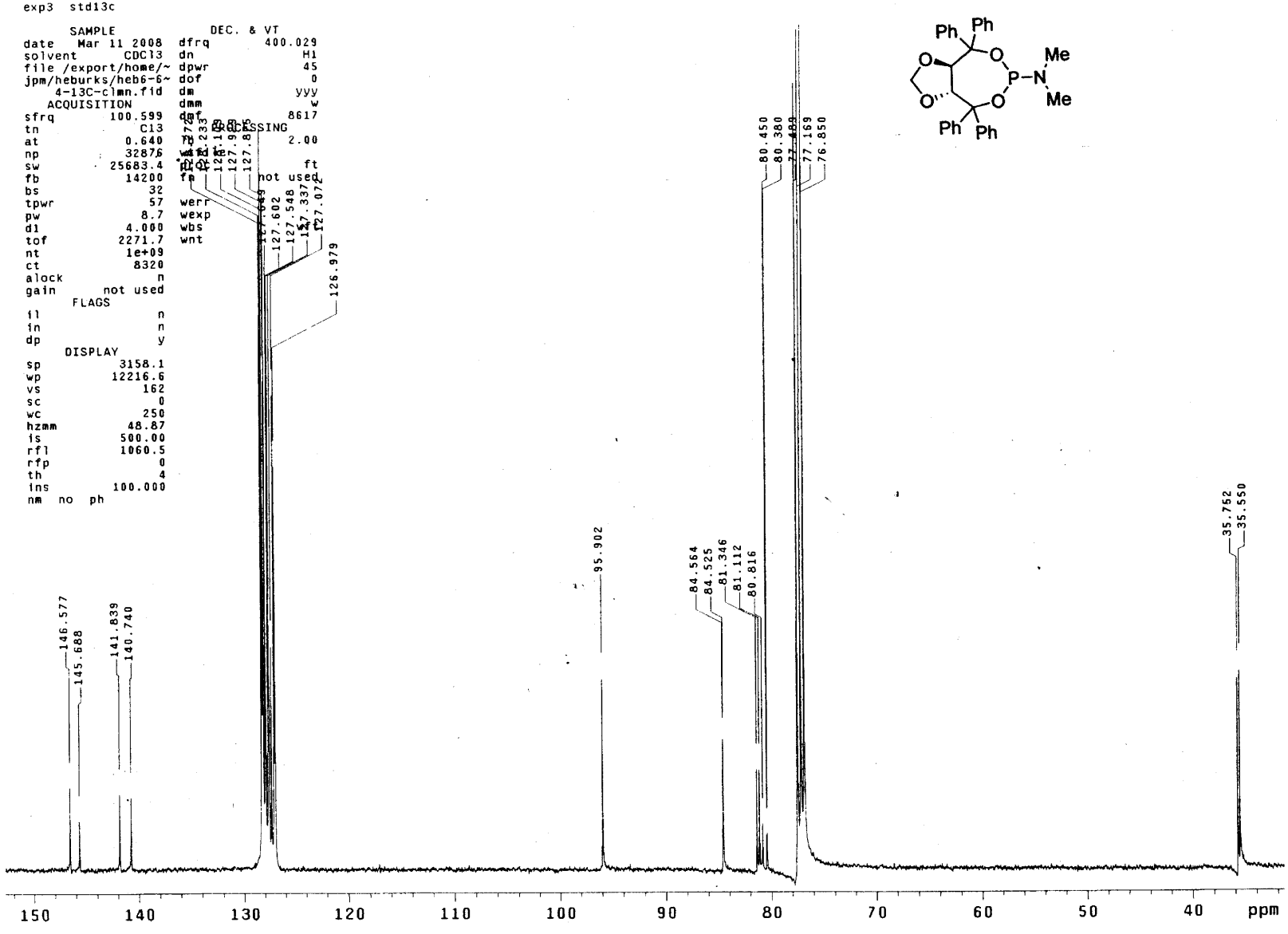
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76.850
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Ph
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O
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40
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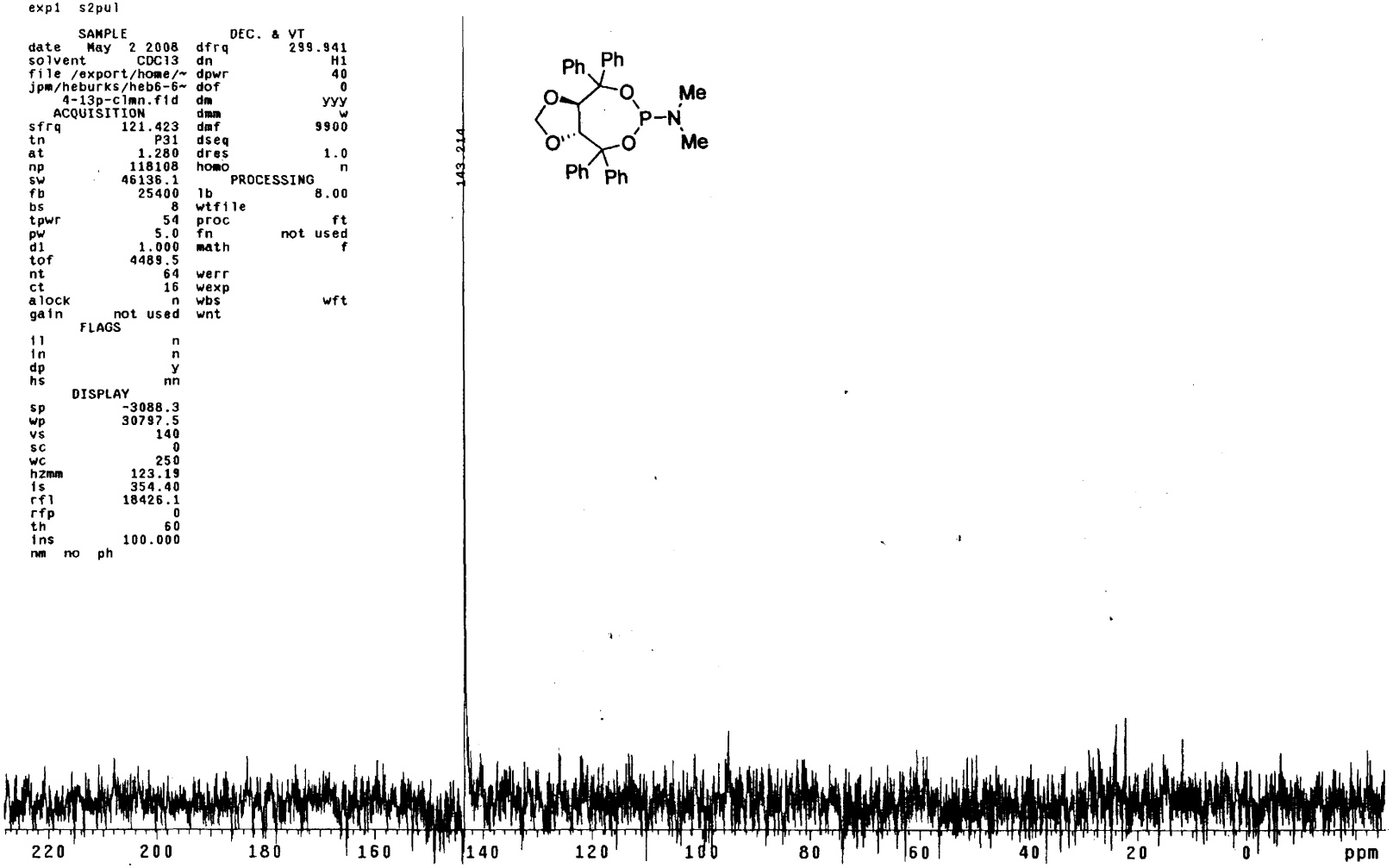

3.5.4.2. General Procedure for (R,R)-TADDOL-Derived Phosphonite Ligands. All TADDOL-derived phosphonites bearing an aryl phosphine were prepared by the following procedure. The following ligands have been previously reported and spectral data are in accordance with the literature. **(*R*,*R*)-3.33**,[29] **(*R*,*R*)-3.34**,[29] **(*R*,*R*)-3.39**,[30] **(*R*,*R*)-3.40**,[30] **(*R*,*R*)-3.46**.[31]

Preparation of (3a*R*,8a*R*)-4,4,6,8,8-Pentaphenyl-tetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine. To a 100-mL round-bottomed flask with magnetic stir bar was added oven-dried 4Å molecular sieves. The flask was then flame-dried under vacuum and subsequently filled with nitrogen. The flask was charged with [5-(hydroxy-diphenyl-methyl)-[1,3]dioxolan-4-yl]-diphenyl-methanol (716 mg, 1.632 mmol), tetrahydrofuran (16 mL, 0.1 M), and triethylamine (773 μL, 5.55 mmol). The flask was cooled to 0 °C (ice/water) and allowed to stir for 15 min at which time the flask was charged with dichlorophenylphosphine (243 mL, 1.795 mmol). The reaction mixture was gradually warmed to room temperature and allowed to stir overnight. Diethyl ether was added to the reaction mixture to precipitate triethylamine hydrochloride salts which were then removed by filtration over Celite. Solvent was removed by rotary evaporation to afford a foam which was purified by column chromatography on silica gel with 5% ethyl acetate/hexanes as the eluant. A white solid was isolated in 58% yield (522.7 mg).

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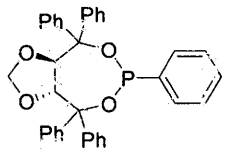
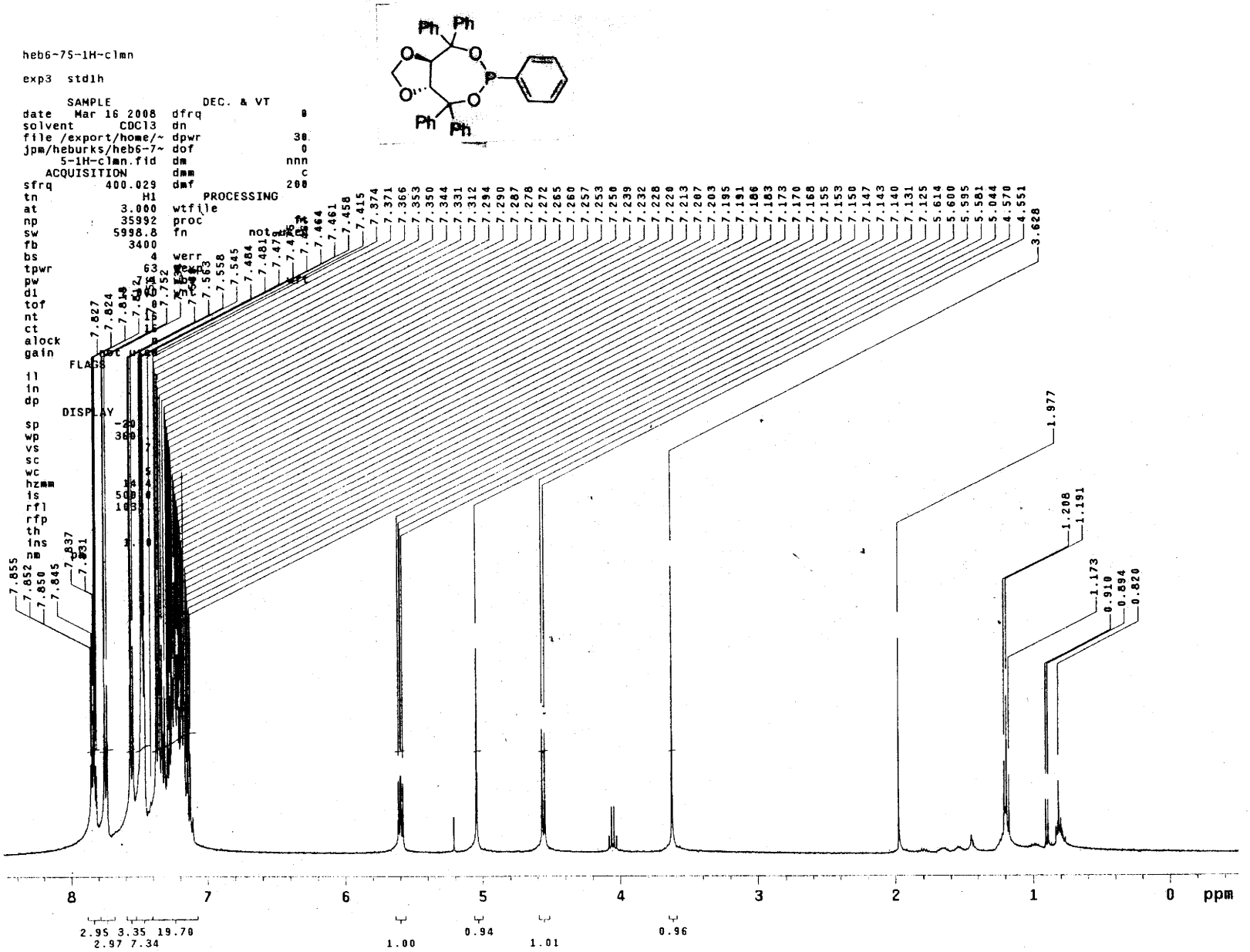
(29) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 4978.
(30) Alexakis, A.; Burton, J.; Vastra, J.; Benhaim, C.; Fournioux, X.; Heuvel, A.; Leveque, J. -M.; Maze, F.; Rosset, S. *Eur. J. Org. Chem.* **2000**, 4011
(31) Sakaki, J.; Schweizer, W. B.; Seebach, D. *Helv. Chim. Acta* **1993**, *76*, 2654.


(*R,R*)-3.35

(3a*R*,8a*R*)-4,4,6,8,8-Pentaphenyl-tetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine (*R,R*)-3.35. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (1H, s, OC**H**$_A$H$_B$O), 4.53 (1H, d, J = 8 Hz, C**H**O), 5.02 (1H, s, OCH$_A$**H**$_B$O), 5.56 (1H, dd, J = 7.6 Hz, J_{HP} = 5.6 Hz, C**H**O), 7.08–7.34 (14H, m, Ar**H**), 7.43 (5H, m, Ar**H**), 7.51-7.53 (2H, m, Ar**H**), 7.56-7.52 (2H, m, Ar**H**), 7.78-7.82 (2H, m, Ar**H**). ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.0 (d, $^{2}J_{CP}$ = 26.5 Hz), 82.4, 82.5, 85.3 (d, $^{3}J_{CP}$ = 3.9 Hz), 96.0, 127.31, 127.34, 127.4, 127.6, 127.71, 127.77, 127.9, 128.1, 128.34, 128.38, 128.4, 128.6 (d, $^{3}J_{CP}$ = 7.1 Hz), 130.0 (d, $^{2}J_{CP}$ = 23.4 Hz), 130.9, 140.1, 140.9 (d, $^{1}J_{CP}$ = 10.9 Hz), 141.3, 145.0, 146.1. ^{31}P NMR (121 MHz, $CDCl_3$) δ 158.3. IR (neat): 3056 (w), 2864 (w), 1598 (m), 1491 (m), 1131 (s), 1035 (s), 693 (s) cm^{-1}. HRMS-(ESI+) for $C_{35}H_{30}O_4P$ calc'd: 545.1882 $(M+H)^+$, observed: 545.1872 $(M+H)^+$. The unpurified reaction mixture was purified on silica gel with 5% ethyl acetate/hexanes as the eluant to afford a white solid in 58% yield (522.7 mg). R_f = 0.50 (10% ethyl acetate, stain in PMA).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gain 60
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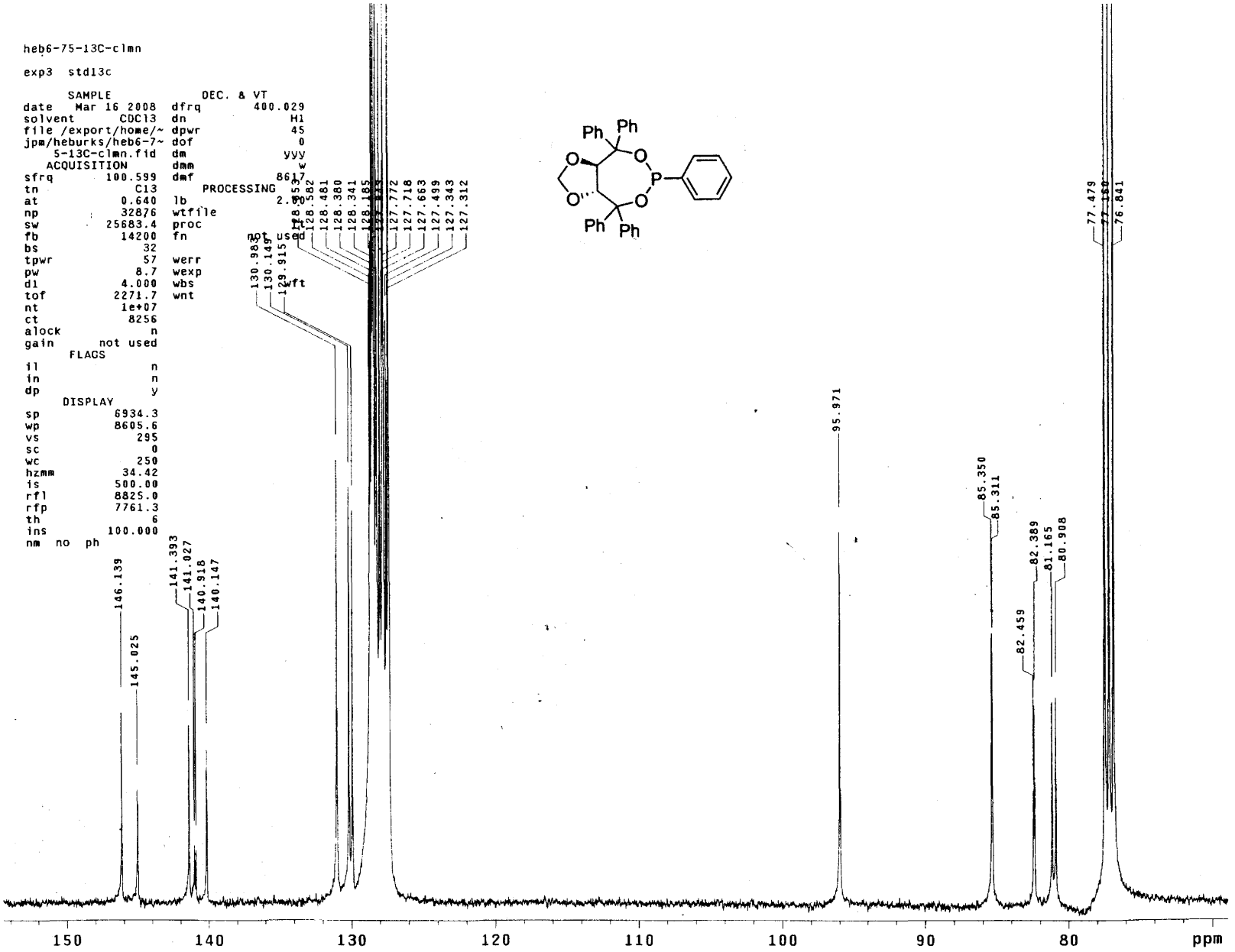
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hzmm 34.42
is 500.00
rfl 8825.0
rfp 7761.3
th 6
ins 100.000
nm no ph
DEC. & VT
dfrq 400.029
dn H1
dpwr 45
dof 0
dm yyy
dmm w
dmf 8617
PROCESSING
lb 2.00
wtfile
proc lb
fn not used
werr
wexp
wbs
wnt
wft
Ph
Ph
O
O
P
O
O
Ph
Ph
146.139
145.025
141.393
141.027
140.918
140.147
130.983
130.149
129.915
128.553
128.482
128.380
128.341
128.185
127.772
127.718
127.663
127.499
127.343
127.312
95.971
85.350
85.311
82.459
82.389
81.165
80.908
77.479
77.160
76.841
150
140
130
120
110
100
90
80
ppm

heb6-75-31p

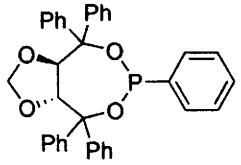
exp1 s2pul

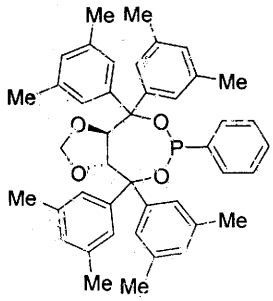
SAMPLE		DEC. & VT	
date	Jul 19 2007	dfrq	299.948
solvent	CDCl3	dn	H1
file	/export/home/~	dpwr	40
	jpm/heburks/heb6-7~	dof	0
	5-31p.fid	dm	yyy
ACQUISITION		dmm	w
sfrq	121.425	dmf	9900
tn	P31	dseq	
at	0.640	dres	1.0
np	128000	homo	n
sw	100000.0	PROCESSING	
fb	49500	lb	2.00
bs	4	wtfile	
tpwr	54	proc	ft
pw	5.0	fn	not used
d1	1.000	math	f
tof	4489.5		
nt	16	werr	
ct	12	wexp	
alock	n	wbs	wft
gain	not used	wnt	

FLAGS	
il	n
in	n
dp	y
hs	nn

DISPLAY	
sp	-2950.2
wp	30879.7
vs	139
sc	0
wc	250
hzmm	123.52
is	354.40
rfl	45358.1
rfp	0
th	20
ins	100.000

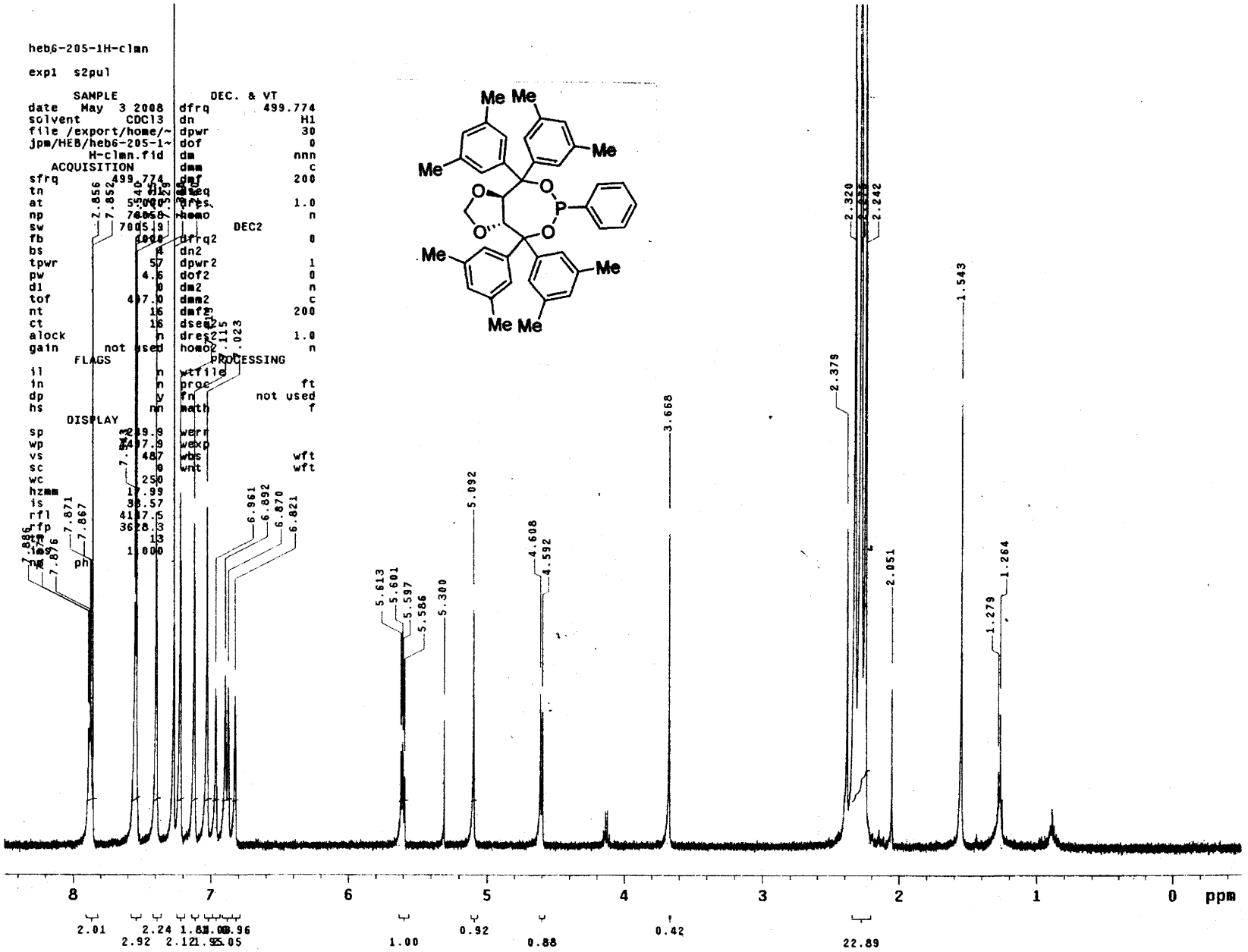
nm no ph

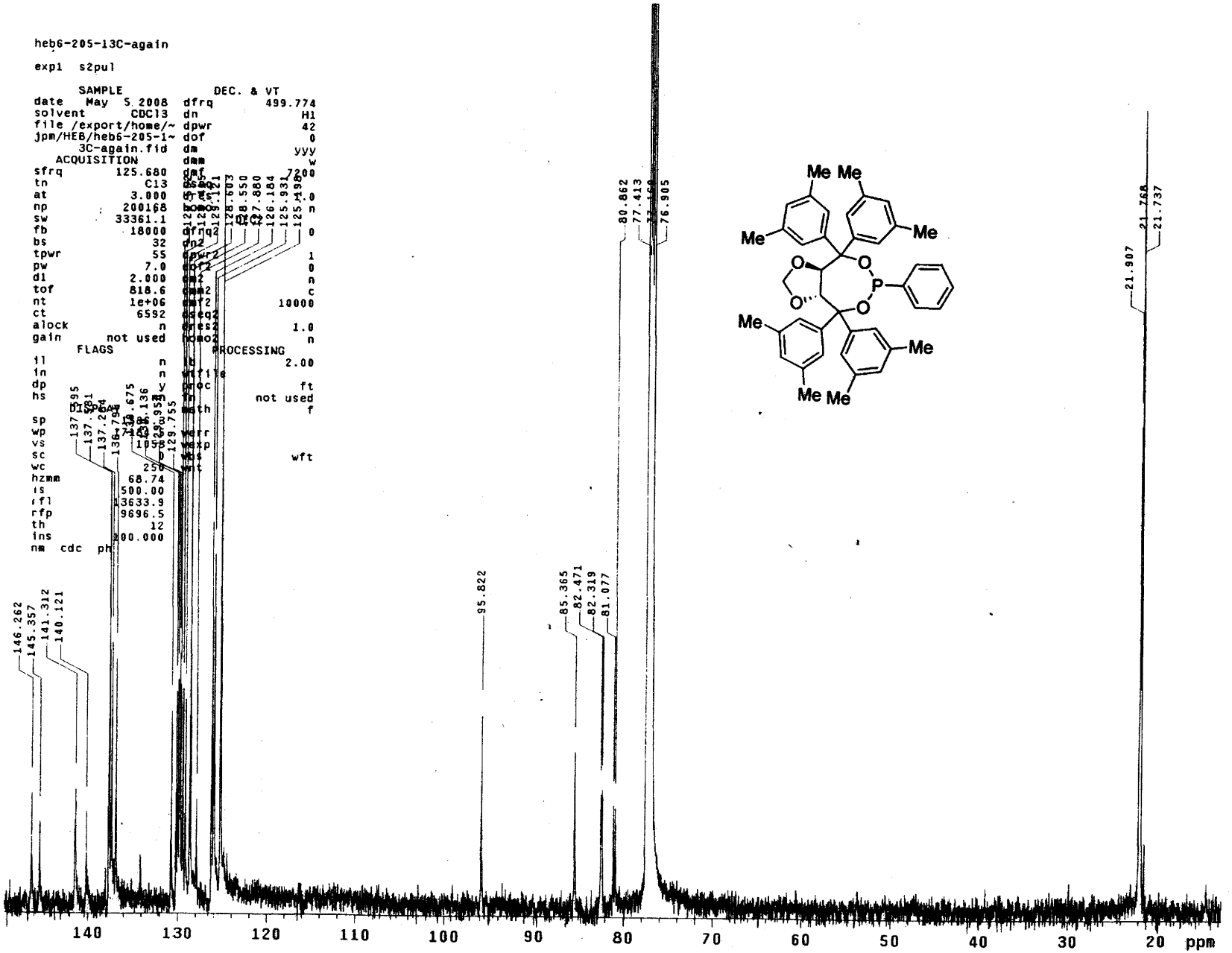




(*R,R*)-3.41

(3a*R*,8a*R*)-4,4,8,8-Tetrakis(3,5-dimethylphenyl)-6-phenyl-tetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine (*R,R*)-3.41. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24 (6H, s, C**H**$_3$Ar), 2.27 (12H, s, C**H**$_3$Ar), 2.32 (6H, s, C**H**$_3$Ar), 3.66 (1H, s, OC**H**$_A$H$_B$O), 4.60 (1H, d, J = 8 Hz, C**H**O), 5.09 (1H, s, OCH$_A$**H**$_B$O), 5.59 (1H, dd, J = 7.5 Hz, J_{HP} = 5.7 Hz, C**H**O), 6.82 (1H, s, Ar**H**), 6.87 (1H, s, Ar**H**), 6.89 (1H, s, Ar**H**), 6.96 (1H, s, Ar**H**), 7.02 (2H, s, Ar**H**), 7.11 (2H, s, Ar**H**), 7.21 (2H, s, Ar**H**), 7.38 (2H, s, Ar**H**), 7.52-7.54 (3H, m, Ar**H**), 7.85-7.88 (2H, m, Ar**H**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 21.73, 21.76, 21.9, 80.9 (d, $^{3}J_{CP}$ = 27 Hz), 82.3, 82.4 (d, $^{2}J_{CP}$ = 6.8 Hz), 85.3, 95.3, 125.2, 125.9, 126.1, 127.8, 128.5 (d, $^{3}J_{CP}$ = 6.6 Hz), 129.1, 129.4, 129.6, 129.8 (d, $^{2}J_{CP}$ = 25.1 Hz), 130.1, 130.6, 134.0, 136.8, 137.2, 137.53, 137.59, 140.1, 141.3, 141.4, 145.3, 146.2. ^{31}P NMR (121 MHz, $CDCl_3$) δ 158.3. IR (neat): 3006 (w), 2912 (w), 2816 (w), 1701 (s), 1600 (s), 1345 (s), 1157 (s), 937 (s), 823 (s), 756 (s) cm^{-1}. HRMS-(ESI+): for $C_{43}H_{46}O_4P$ calc'd: 657.3134 $(M+H)^+$, observed: 657.3130 $(M+H)^+$. The unpurified reaction mixture was purified on silica gel with 5% ethyl acetate/hexanes as the eluant to afford a white solid in 28% yield (340.9 mg). R_f = 0.31 (10% ethyl acetate, stain in PMA).

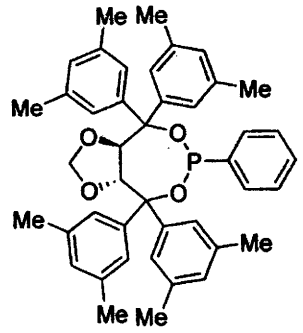

heb6-205-1H-clmn
expl s2pul
SAMPLE
date May 3 2008
solvent CDCl3
file /export/home/~
jpm/HEB/heb6-205-1~
H-clmn.fid
ACQUISITION
sfrq 499.774
tn H1
at 5.000
np 76858
sw 7005.9
fb 4000
bs 4
tpwr 57
pw 4.6
dl 0
tof 497.0
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp 239.9
wp 7497.9
vs 487
sc 0
wc 250
hzmm 17.99
is 38.57
rfl 4187.5
rfp 3628.3
th 13
lb 1.000
pp
DEC. & VT
dfrq 499.774
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
dseq
dres 1.0
homo n
DEC2
dfrq2 0
dn2
dpwr2 1
dof2 0
dm2 n
dmm2 c
dmf2 200
dseq2
dres2 1.0
homo2 n
PROCESSING
wtfile
proc ft
fn not used
math f
wexp
wbs wft
wnt wft
Me
O
P
7.886
7.876
7.871
7.867
6.961
6.892
6.870
6.821
5.613
5.601
5.597
5.586
5.300
5.092
4.608
4.592
3.668
2.379
2.320
2.242
2.051
1.543
1.279
1.264
8
7
6
5
4
3
2
1
0
ppm
2.01
2.24
1.81
1.00
0.92
0.88
0.42
22.89

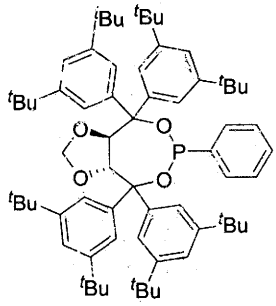

heb6-205-13C-again
expl s2pul
SAMPLE
date May 5 2008
solvent CDCl3
file /export/home/~
jpm/HEB/heb6-205-1~
3C-again.fid
ACQUISITION
sfrq 125.680
tn C13
at 3.000
np 200168
sw 33361.1
fb 18000
bs 32
tpwr 55
pw 7.0
d1 2.000
tof 818.6
nt 1e+06
ct 6592
alock n
gain not used
FLAGS
DEC. & VT
dfrq 499.774
dn H1
dpwr 42
dof 0
dm yyy
dmf 7200
dpwr2 1
dof2 0
dm2 c
nt2 10000
cpd2
tof2 1.0
gain2 n
PROCESSING
lb 2.00
wtfile
proc ft
fn not used
math f
werr
wexp
wbs wft
wnt
hzmm 68.74
is 500.00
rfl 3633.9
rfp 9696.5
th 12
ins 200.000
nm cdc ph
146.262
145.357
141.312
140.121
95.822
85.365
82.471
82.319
81.077
80.862
77.413
76.905
21.907
21.768
21.737
Me Me
Me
Me
Me
Me
Me Me
O
O
O
O
P
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

heb6-205-clmn-31p

expi s2pul

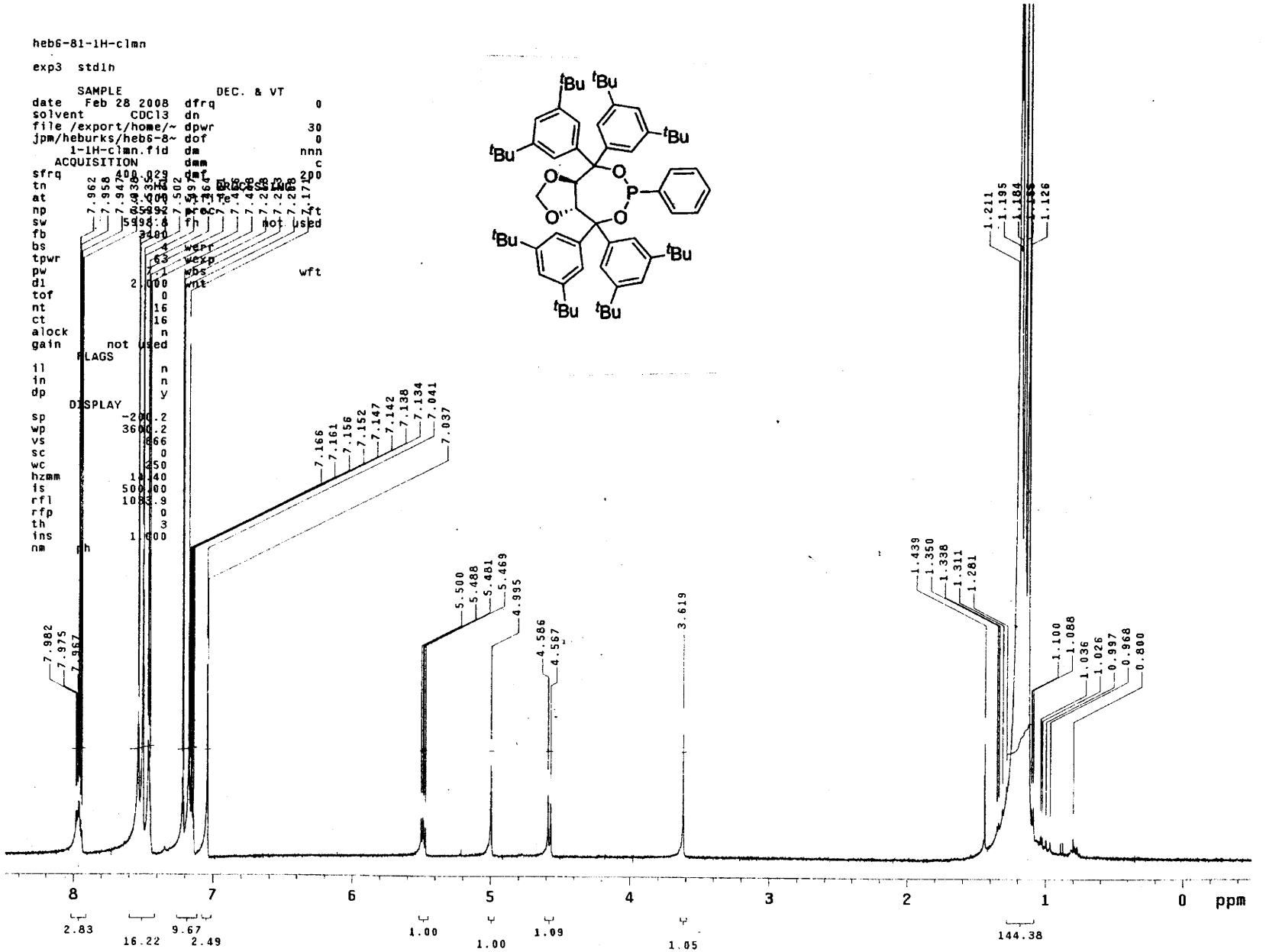
SAMPLE		DEC. & VT	
date	Oct 27 2007	dfrq	299.948
solvent	CDCl3	dn	H1
file	/export/home/~	dpwr	40
	jpm/heburks/heb6-2~	dof	0
	05-clmn-31p.fid	dm	yyy
ACQUISITION		dmm	w
sfrq	121.425	dmf	9900
tn	P31	dseq	
at	0.640	dres	1.0
np	128000	homo	n
sw	100000.0	PROCESSING	
fb	49500	lb	4.00
bs	8	wtfile	
tpwr	54	proc	ft
pw	5.0	fn	not used
d1	1.000	math	f
tof	4489.5		
nt	64	werr	
ct	64	wexp	
alock	n	wbs	wft
gain	not used	wnt	
FLAGS			
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-1995.0		
wp	30748.5		
vs	140		
sc	0		
wc	250		
hzmm	122.99		
is	354.40		
rfl	45358.1		
rfp	0		
th	20		
ins	100.000		
nm no ph			

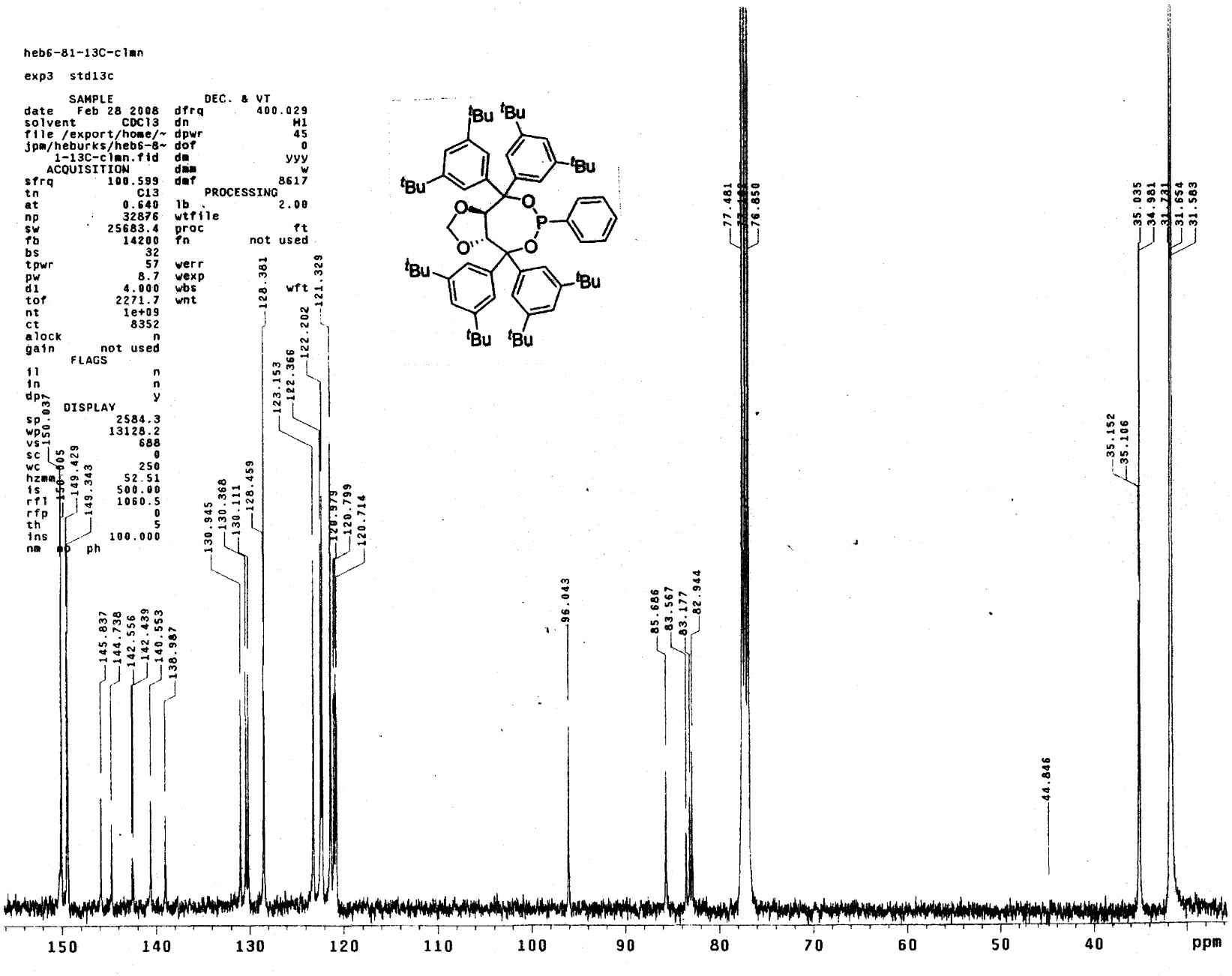




(*R,R*)-3.36

(3a*R*,8a*R*)-4,4,8,8-Tetrakis(3,5-di-*tert*-butylphenyl)-6-phenyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine (*R,R*)-3.36. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12-1.21 (72H, m, $(CH_3)_3C$ x 9), 3.61 (1H, s, OCH_AH_BO), 4.57 (1H, d, J = 7.6 Hz, CHO), 4.99 (1H, s, OCH_AH_BO), 5.48 (1H, dd, J = 7.6 Hz, J_{HP} = 4.8 Hz, CHO), 7.04 (1H, d, J = 1.6 Hz, ArH), 7.13-7.28 (5H, m, ArH), 7.48-7.53 (9H, m, ArH), 7.94-7.98 (2H, m, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.5, 31.6, 31.7, 34.9, 35.0, 35.1, 35.2, 82.9, 83.1, 83.5, 85.6, 96.0, 120.7, 120.8, 120.9, 121.3, 122.2, 122.3, 123.1, 128.4 (d, $^{3}J_{CP}$ = 7.8 Hz), 130.2 (d, $^{2}J_{CP}$ = 25.7 Hz), 130.9, 138.9, 140.5, 142.5 (d, $^{1}J_{CP}$ = 11.7 Hz), 144.7, 145.8, 149.3, 149.4, 150.00, 150.03. ^{31}P NMR (121 MHz, $CDCl_3$) δ 157.6. IR (neat): 2958 (s), 2903 (m), 2865 (s), 1597 (s), 1477 (s), 1451 (s), 1437 (s), 1362 (s), 1007 (s), 864 (s) cm^{-1}. HRMS-(ESI+): for $C_{67}H_{93}O_4NaP$ calc'd: 1015.6709 $(M+Na)^+$, observed: 1015.6750 $(M+Na)^+$. The unpurified reaction mixture was purified on silica gel with 5% ethyl acetate/hexanes as the eluant to afford a white solid in 18% yield (119.1 mg). R_f = 0.84 (10% ethyl acetate, stain in PMA)

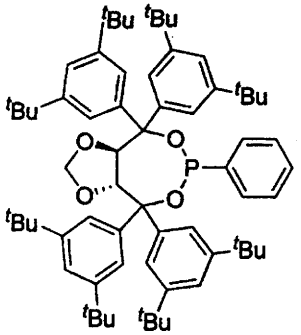

heb6-81-1H-clmn
exp3 stdlh
SAMPLE
date Feb 28 2008
solvent CDCl3
file /export/home/~
jpm/heburks/heb6-8~
1-1H-clmn.fid
ACQUISITION
DEC. & VT
DISPLAY
FLAGS
not used
not used
wft
7.982
7.975
7.967
7.962
7.958
7.947
7.502
7.166
7.161
7.156
7.152
7.147
7.142
7.138
7.134
7.041
7.037
5.500
5.488
5.481
5.469
4.995
4.586
4.567
3.619
1.439
1.350
1.338
1.311
1.281
1.211
1.195
1.126
1.100
1.088
1.036
1.026
0.997
0.968
0.800
8
7
6
5
4
3
2
1
0
ppm
2.83
16.22
9.67
2.49
1.00
1.00
1.09
1.05
144.38

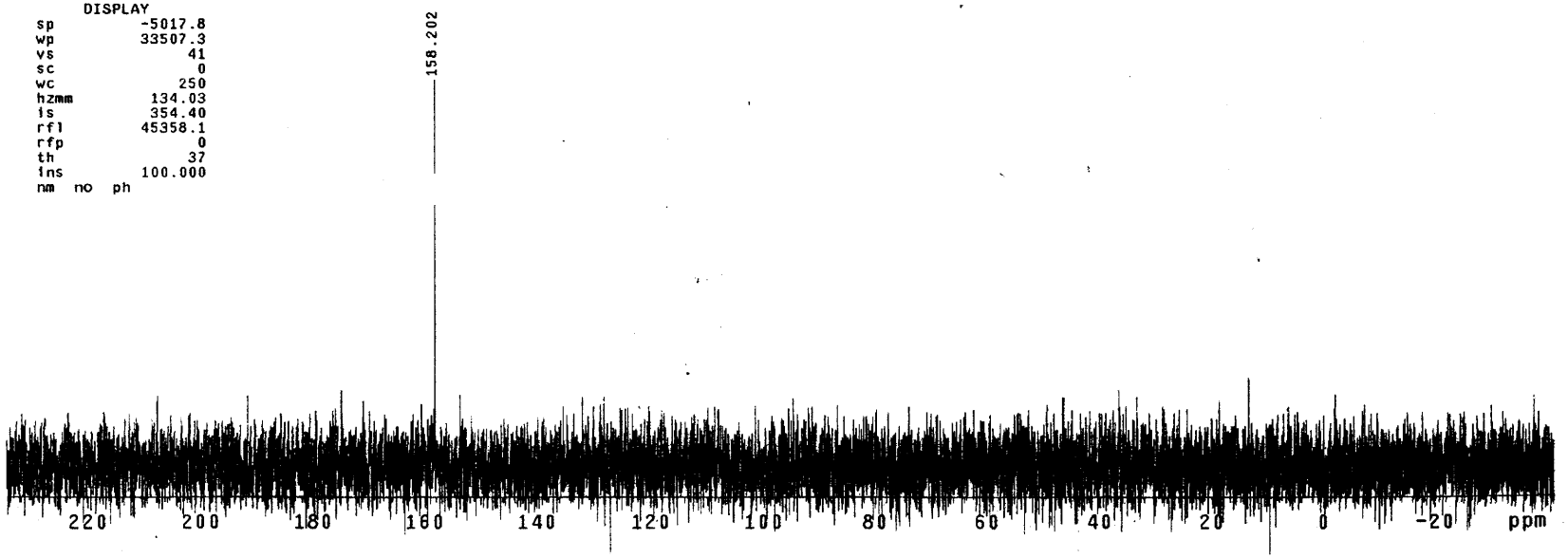

heb6-81-13C-clmn
exp3 std13c
SAMPLE
date Feb 28 2008
solvent CDCl3
file /export/home/~
jpm/heburks/heb6-8~
1-13C-clmn.fid
ACQUISITION
sfrq 100.599
tn C13
at 0.640
np 32876
sw 25683.4
fb 14200
bs 32
tpwr 57
pw 8.7
d1 4.000
tof 2271.7
nt 1e+09
ct 8352
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp 2584.3
wp 13128.2
vs 688
sc 0
wc 250
hzmm 52.51
is 500.00
rfl 1060.5
rfp 0
th 5
ins 100.000
nm pp ph
DEC. & VT
dfrq 400.029
dn H1
dpwr 45
dof 0
dm yyy
dmm w
dmf 8617
PROCESSING
lb 2.00
wtfile
proc ft
fn not used
werr
wexp
wbs wft
wnt
tBu
O
P
150.037
150.005
149.429
149.343
145.837
144.738
142.556
142.439
140.553
138.987
130.945
130.368
130.111
128.459
128.381
123.153
122.366
122.202
121.329
120.979
120.799
120.714
96.043
85.686
83.567
83.177
82.944
77.481
76.850
44.846
35.152
35.106
35.035
34.981
31.731
31.654
31.583
150
140
130
120
110
100
90
80
70
60
50
40
ppm

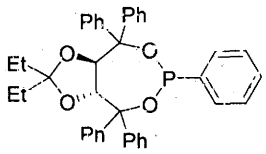
heb6-81-31p

exp1 s2pul

SAMPLE		DEC. & VT	
date	Jul 24 2007	dfrq	299.948
solvent	CDCl3	dn	H1
file	/export/home/~	dpwr	40
jpm/heburks/heb6-8~		dof	0
	1-31p.fid	dm	yyy
ACQUISITION		dmm	w
sfrq	121.425	dmf	9900
tn	P31	dseq	
at	0.640	dres	1.0
np	128000	homo	n
sw	100000.0	PROCESSING	
fb	49500	lb	2.00
bs	4	wtfile	
tpwr	54	proc	ft
pw	5.0	fn	not used
d1	1.000	math	f
tof	4489.5		
nt	164	werr	
ct	52	wexp	
alock	n	wbs	wft
gain	not used	wnt	
FLAGS			
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-5017.8		
wp	33507.3		
vs	41		
sc	0		
wc	250		
hzmm	134.03		
is	354.40		
rfl	45358.1		
rfp	0		
th	37		
ins	100.000		
nm no ph			

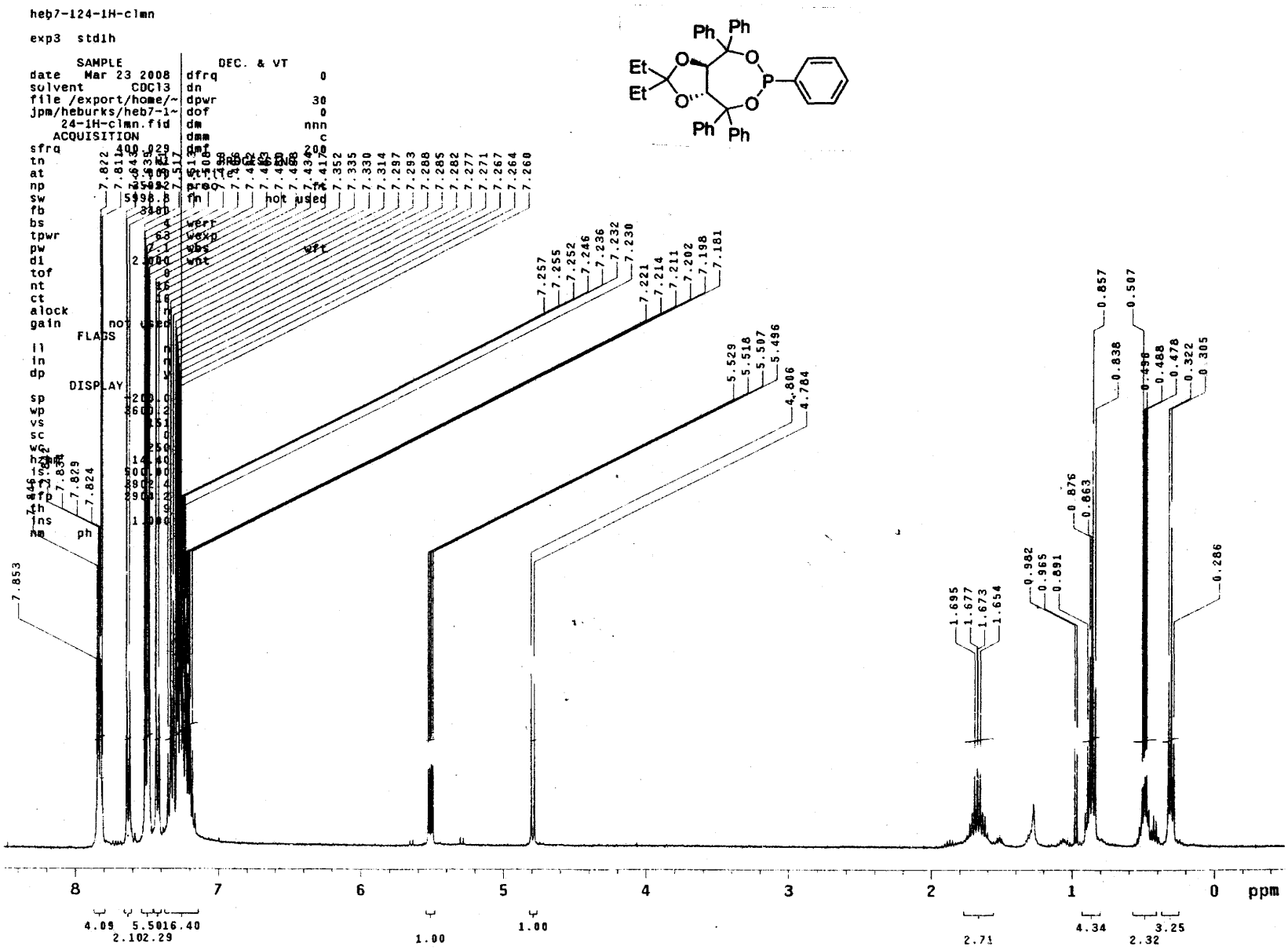


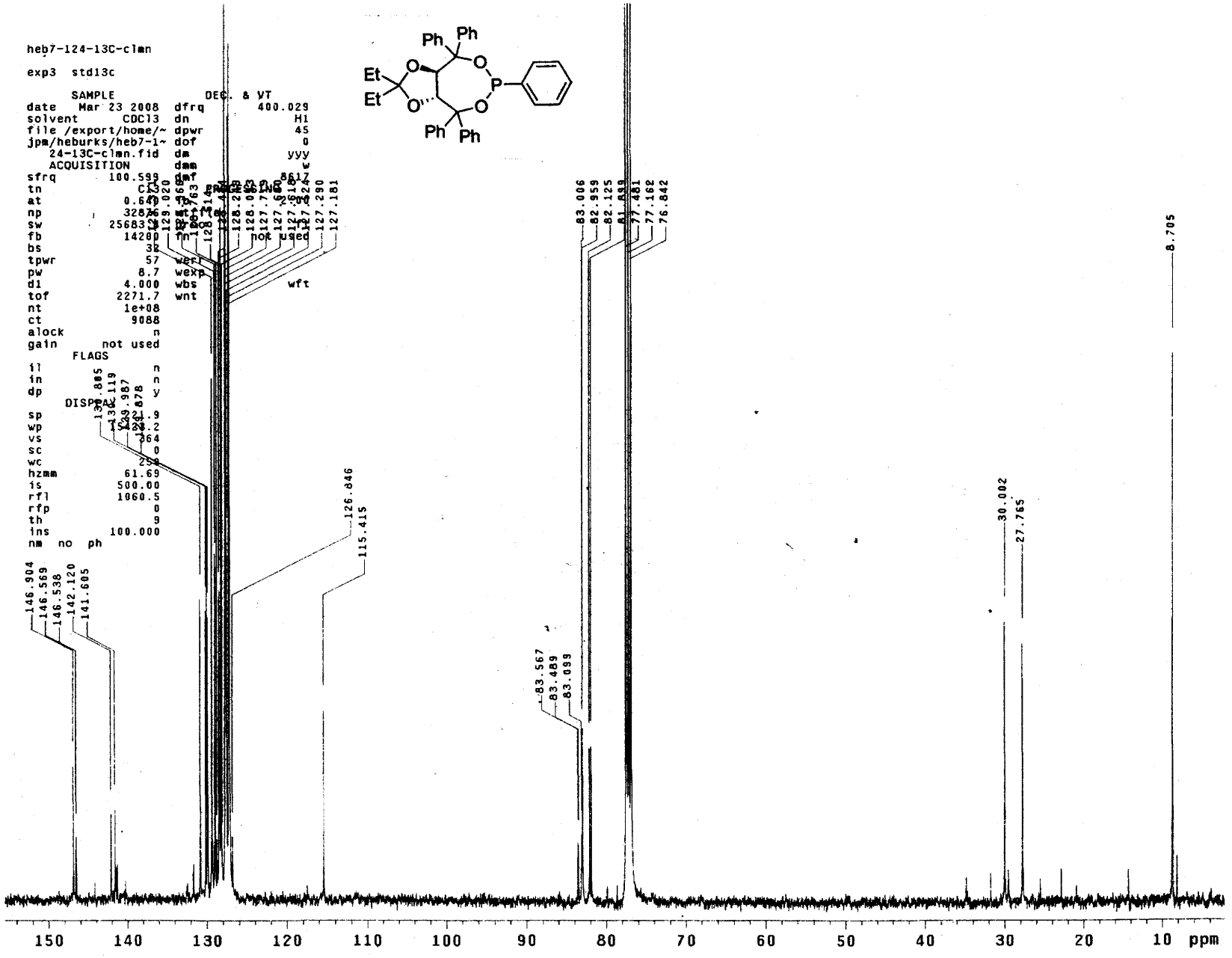




(*R,R*)-3.42

(3a*R*,8a*R*)-2.2-Diethyl-4,4,6,8,8-pentaphenyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine (*R,R*)-3.42. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.30 (3H, t, J = 7.6 Hz, C**H**$_3$CH$_2$), 0.85 (3H, t, J = 7.6 Hz, C**H**$_3$CH$_2$), 1.61-1.72 (4H, m, CH$_3$C**H**$_2$), 4.70 (1H, d, J = 8.8 Hz, C**H**O), 5.42 (1H, dd, J = 8.8 Hz, J_{HP} = 4.4 Hz, C**H**O), 7.09-7.26 (12H, m, Ar**H**), 7.32-7.34 (2H, m, Ar**H**), 7.39-7.42 (5H, m, Ar**H**), 7.53-7.55 (2H, m, Ar**H**), 7.72-7.76 (4H, m, Ar**H**). ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.7, 27.7, 30.0, 82.0 (d, $^{3}J_{CP}$ = 22.6 Hz), 82.9 (d, $^{2}J_{CP}$ = 4.6 Hz), 83.0, 83.5 (d, $^{2}J_{CP}$ = 7.8 Hz), 115.4, 127.1, 127.2, 127.5, 127.61, 127.67, 127.7, 128.2, 128.4 (d, $^{3}J_{CP}$ = 7 Hz), 128.9, 129.0, 129.3, 129.9 (d, $^{2}J_{CP}$ = 24 Hz), 130.8, 141.4 (d, $^{1}J_{CP}$ = 11.7 Hz), 141.6, 142.1, 146.5 (d, $^{3}J_{CP}$ = 3.1 Hz), 146.9. ^{31}P NMR (121 MHz, $CDCl_3$) δ 157.8. IR (neat): 3058 (w), 2970 (w), 2939 (w), 1492 (m), 1446 (m), 694 (s) cm^{-1}. HRMS-(ESI+): for $C_{39}H_{38}O_4P$ calc'd: 601.2517 $(M+H)^+$, observed: 601.2517 $(M+H)^+$. The unpurified reaction mixture was purified on silica gel with 5% ethyl acetate/hexanes as the eluant to afford a white solid in 58% yield (283 mg). R_f = 0.71 (10% ethyl acetate, stain in PMA).


heb7-124-1H-clmn
exp3 stdlh
SAMPLE
date Mar 23 2008
solvent CDCl3
file /export/home/~
jpm/heburks/heb7-1~
24-1H-clmn.fid
ACQUISITION
DEC. & VT
FLAGS
DISPLAY
Et
Et
Ph
Ph
Ph
Ph
O
O
O
O
P
7.853
7.822
7.811
7.829
7.824
7.517
7.257
7.255
7.252
7.246
7.236
7.232
7.230
7.221
7.214
7.211
7.202
7.198
7.181
5.529
5.518
5.507
5.496
4.806
4.784
1.695
1.677
1.673
1.654
0.982
0.965
0.891
0.876
0.863
0.857
0.838
0.507
0.496
0.488
0.478
0.322
0.305
0.286
8
7
6
5
4
3
2
1
0
ppm
4.09
5.50
16.40
2.10
2.29
1.00
1.00
2.71
4.34
2.32
3.25


heb7-124-13C-clmn
exp3 std13c
SAMPLE
date Mar 23 2008
solvent CDCl3
file /export/home/~
jpm/heburks/heb7-1~
24-13C-clmn.fid
ACQUISITION
sfrq 100.599
tn C13
at 0.643
np 32836
sw 25683.1
fb 14200
bs 32
tpwr 57
pw 8.7
d1 4.000
tof 2271.7
nt 1e+08
ct 9088
alock n
gain not used
FLAGS
il n
in n
dp y
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wp 4228.2
vs 364
sc 0
wc 250
hzmm 61.69
is 500.00
rfl 1060.5
rfp 0
th 9
ins 100.000
nm no ph
DEC. & VT
dfrq 400.029
dn H1
dpwr 45
dof 0
dm yyy
dmm w
dmf 8617
wft
wexp
wbs
wnt
not used
Ph
Et
O
P
146.904
146.569
146.538
142.120
141.605
126.846
115.415
83.567
83.489
83.099
83.006
82.959
82.125
77.481
77.162
76.842
30.002
27.765
8.705
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

heb7-124-31P-clmn

expl s2pul

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date	Mar 22 2008	dfrq	299.948
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ACQUISITION		dmm	w
sfrq	121.425	dmf	9900
tn	P31	dseq	
at	1.280	dres	1.0
np	118108	homo	n
sw	46136.1	PROCESSING	
fb	25400	lb	8.00
bs	8	wtfile	
tpwr	54	proc	ft
pw	5.0	fn	not used
d1	1.000	math	f
tof	4489.5		
nt	64	werr	
ct	16	wexp	
alock	n	wbs	wft
gain	not used	wnt	

FLAGS	
il	n
in	n
dp	y
hs	nn

DISPLAY	
sp	-2421.6
wp	30070.3
vs	140
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rfp	0
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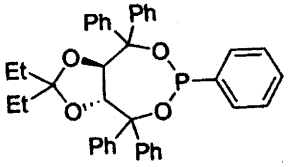
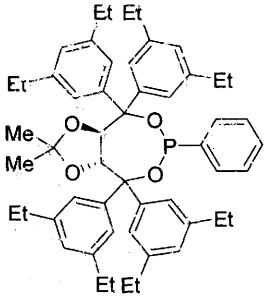
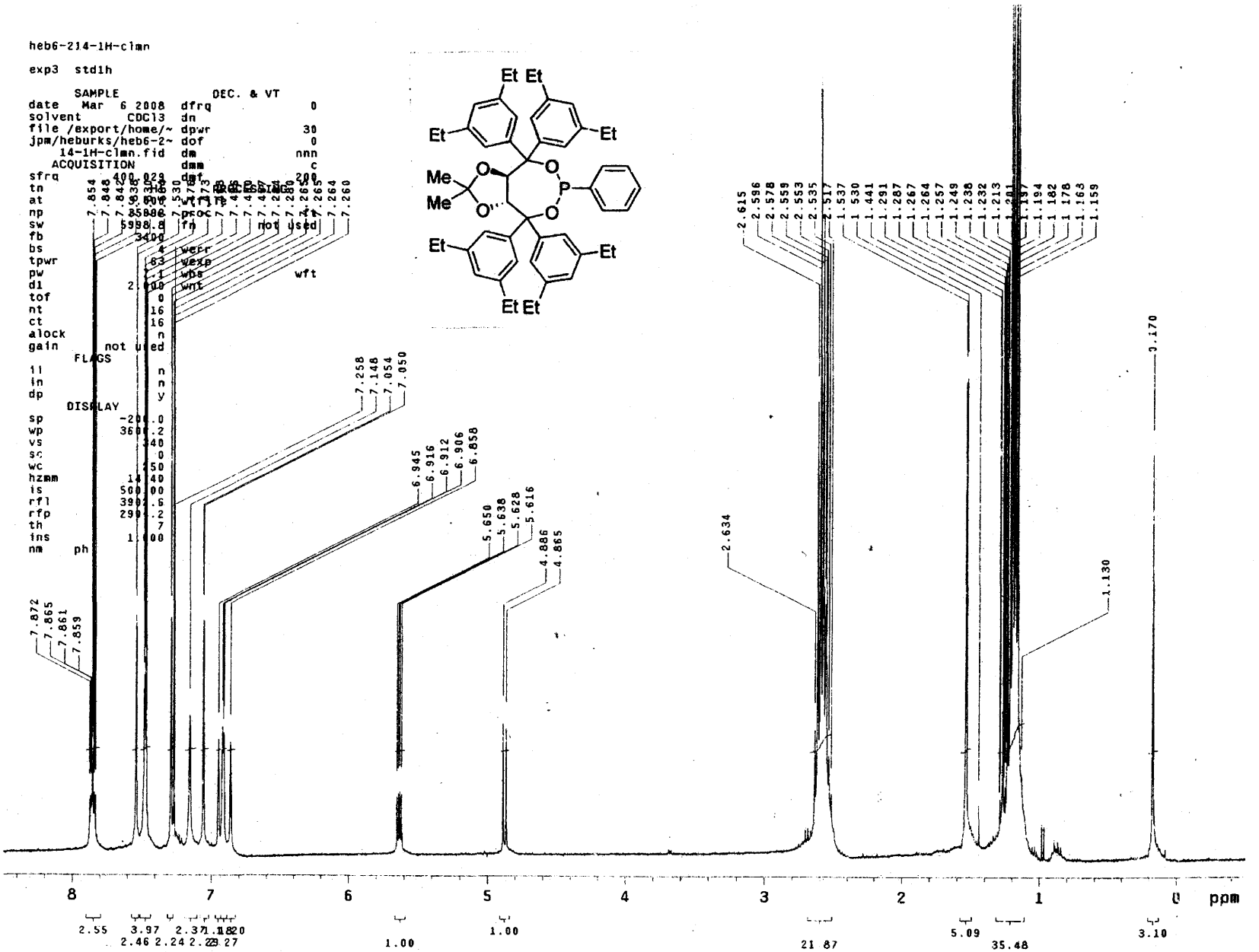
nm no ph	





(*R,R*)-3.37

(3a*R*,8a*R*)-4,4,8,8-Tetrakis(3,5-diethylphenyl)-2,2-dimethyl-6-phenyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine (*R,R*)-3.37. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.17 (3H, s, $(CH_3)_2C$), 1.15-1.23 (24H, m, CH_3CH_2Ar), 1.53 (3H, s, $(CH_3)_2C$), 2.53-2.63 (CH_3CH_2Ar), 4.87 (1H, d, J = 8.4 Hz, CHO), 5.63 (1H, dd, J = 8.8 Hz, J_{HP} = 4.8 Hz, CHO), 6.85 (1H, s, ArH), 6.90-6.91 (2H, m, ArH), 6.94 (1H, s, ArH), 7.05 (2H, d, J = 1.6 Hz, ArH), 7.14 (2H, s, ArH), 7.28 (2H, d, J = 1.6 Hz, ArH), 7.45-7.47 (3H, m, ArH), 7.53 (2H, d, J = 1.6 Hz, ArH), 7.83-7.87 (2H, m, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 15.6, 15.8, 16.0, 24.8, 28.1, 29.0, 29.1, 29.3, 82.6, 83.0 (d, $^{3}J_{CP}$ = 23.2 Hz), 83.7 (d, $^{2}J_{CP}$ = 7 Hz), 84.4 (d, $^{3}J_{CP}$ = 3.9 Hz), 111.0, 124.6, 124.7, 126.0, 126.4, 126.5, 126.6, 126.7, 128.2 (d, $^{3}J_{CP}$ = 7 Hz), 130.0 (d, $^{2}J_{CP}$ = 24.4 Hz), 130.4, 141.6, 141.7, 142.0 (d, $^{1}J_{CP}$ = 11.6 Hz), 142.7, 143.0, 143.4, 143.6, 146.4 (d, $^{3}J_{CP}$ = 1.9 Hz), 147.0. ^{31}P NMR (121 MHz, $CDCl_3$) δ 156.2. IR (neat): 2962 (s), 2930 (s), 2871 (s), 1598 (s), 1456 (s), 1062 (s), 1035 (s), 873 (s), 718 (s) cm^{-1}. HRMS-(ESI+): for $C_{53}H_{65}O_4NaP$ calc'd: 819.4518 $(M+Na)^+$, observed: 819.4511 $(M+Na)^+$. The unpurified reaction mixture was purified on silica gel with 5% ethyl acetate/hexanes as the eluant to afford a white solid in 36% yield (210.3 mg). R_f = 0.62 (10% ethyl acetate, stain in PMA).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date Mar 6 2008
solvent CDCl3
file /export/home/~
jpm/heburks/heb6-2~
14-1H-clmn.fid
ACQUISITION
DEC. & VT
FLAGS
DISPLAY
Et Et
Et
Et
Me
Me
O
O
O
O
P
Et
Et
Et Et
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7.865
7.861
7.859
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7.054
7.050
6.945
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6.912
6.906
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5.650
5.638
5.628
5.616
4.886
4.865
2.634
2.615
2.596
2.578
2.559
2.553
2.535
2.517
1.537
1.530
1.441
1.291
1.287
1.267
1.264
1.257
1.249
1.238
1.232
1.213
1.194
1.182
1.178
1.163
1.159
1.130
3.170
8
7
6
5
4
3
2
1
0
ppm
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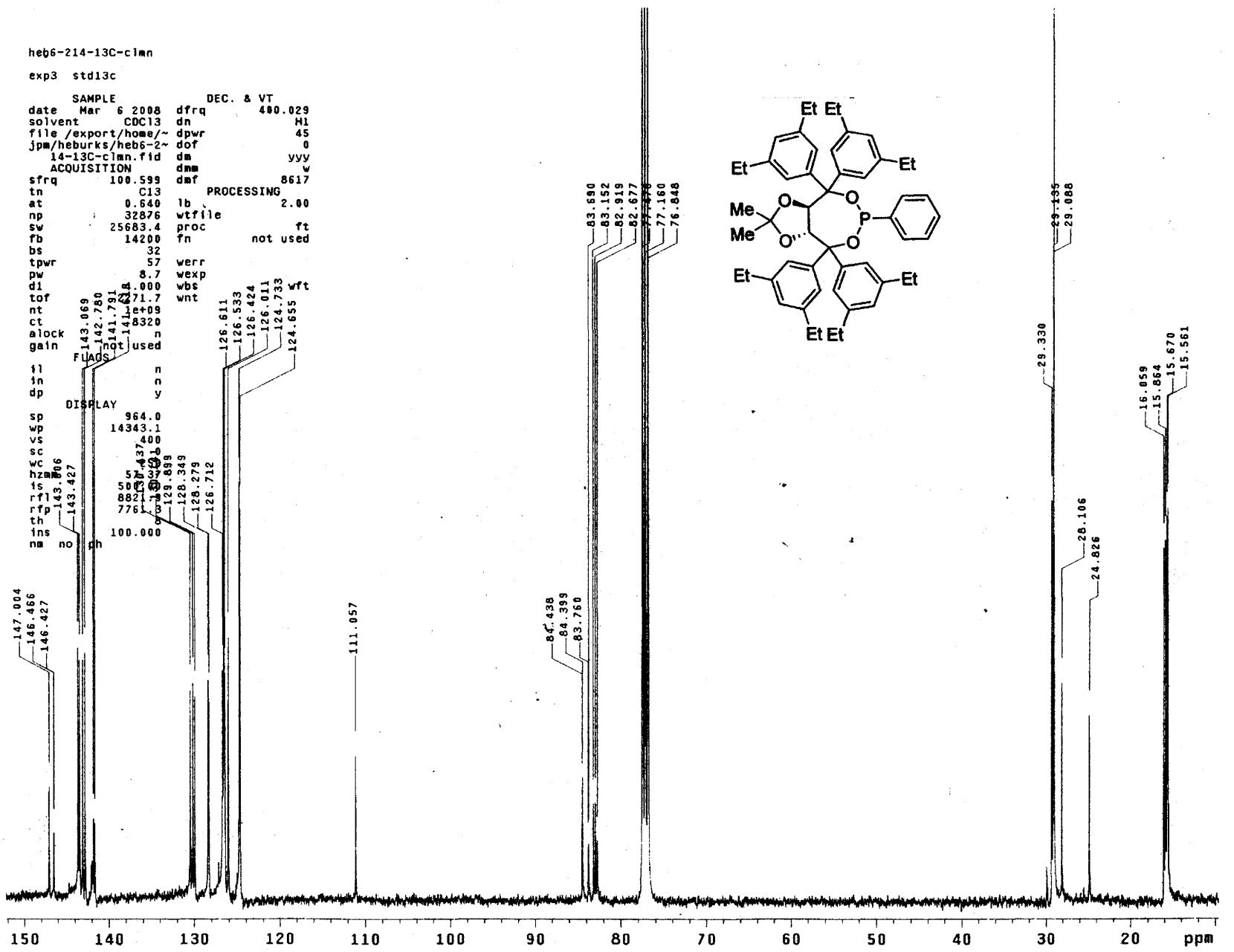
3.97
2.46
2.24
2.37
1.00
1.00
21.87
5.09
35.48
3.10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date Mar 6 2008
solvent CDCl3
file /export/home/~
jpm/heburks/heb6-2~
14-13C-clmn.fid
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np 32876
sw 25683.4
fb 14200
bs 32
tpwr 57
pw 8.7
d1 4.000
tof 271.7
nt 1e+09
ct 8320
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
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wp 14343.1
vs 400
sc
wc
hzmm
is 50
rfl 8821
rfp 7761
th
ins 100.000
nm no ph
DEC. & VT
dfrq 400.029
dn H1
dpwr 45
dof 0
dm yyy
dmm w
dmf 8617
PROCESSING
lb 2.00
wtfile
proc ft
fn not used
werr
wexp
wbs
wnt wft
Et Et
Et
Et
Me
Me
O
O
P
O
O
Et
Et
Et Et
147.004
146.466
146.427
143.427
143.069
142.780
141.791
126.611
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126.424
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124.733
124.655
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111.057
84.438
84.399
83.760
83.690
83.152
82.919
82.677
77.160
76.848
29.330
29.135
29.088
28.106
24.826
16.059
15.864
15.670
15.561
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

P-31 STANDARD PARAMETERS
PHOSPHATE REGION

exp1 s2pul

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sw	100000.0	PROCESSING	
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bs	16	wtfile	
tpwr	54	proc	ft
pw	5.0	fn	not used
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tof	4489.5		
nt	1	werr	
ct	1	wexp	
alock	n	wbs	wft
gain	not used	wnt	
FLAGS			
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-4491.3		
wp	37055.0		
vs	139		
sc	0		
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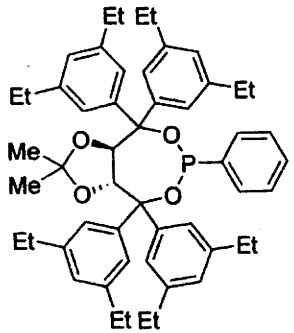
ins	100.000		
nm no ph			

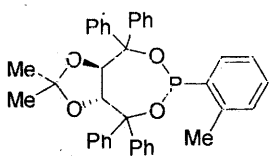


3.5.4.3. General Procedure for (R,R)-TADDOL-Derived Phosphonites with Substituted Aryl Phosphines.

Preparation of (3aR,8aR)-2,2-Dimethyl-4,4,8,8-tetraphenyl-6-o-tolyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine. The following procedure was adapted from a previously reported procedure by Seebach.[31] To a 100-mL round-bottomed flask with magnetic stir bar was added bis(diethylamino)phosphorus (500 μL, 2.37 mmol) chloride and diethyl ether (7.4 mL, 0.32 M). The flask was cooled to -78 °C (dry ice/isopropanol) and charged with *ortho*-methyl phenyl magnesium bromide (4.5 mL, 0.58 M) over the course of 1 h. The reaction mixture was gradually warmed to room temperature and allowed to stir overnight. The flask was then cooled to 0 °C (ice/water) and slowly charged with hydrogen chloride in diethyl ether (7.1 mL, 6.0 equiv) over the course of 1 h. The reaction mixture was allowed to stir for an additional 2 h at which time the solids were removed by cannula filtration into a flame-dried round-bottomed flask. Volatiles were removed *in vacuo* to reveal a yellow oil.

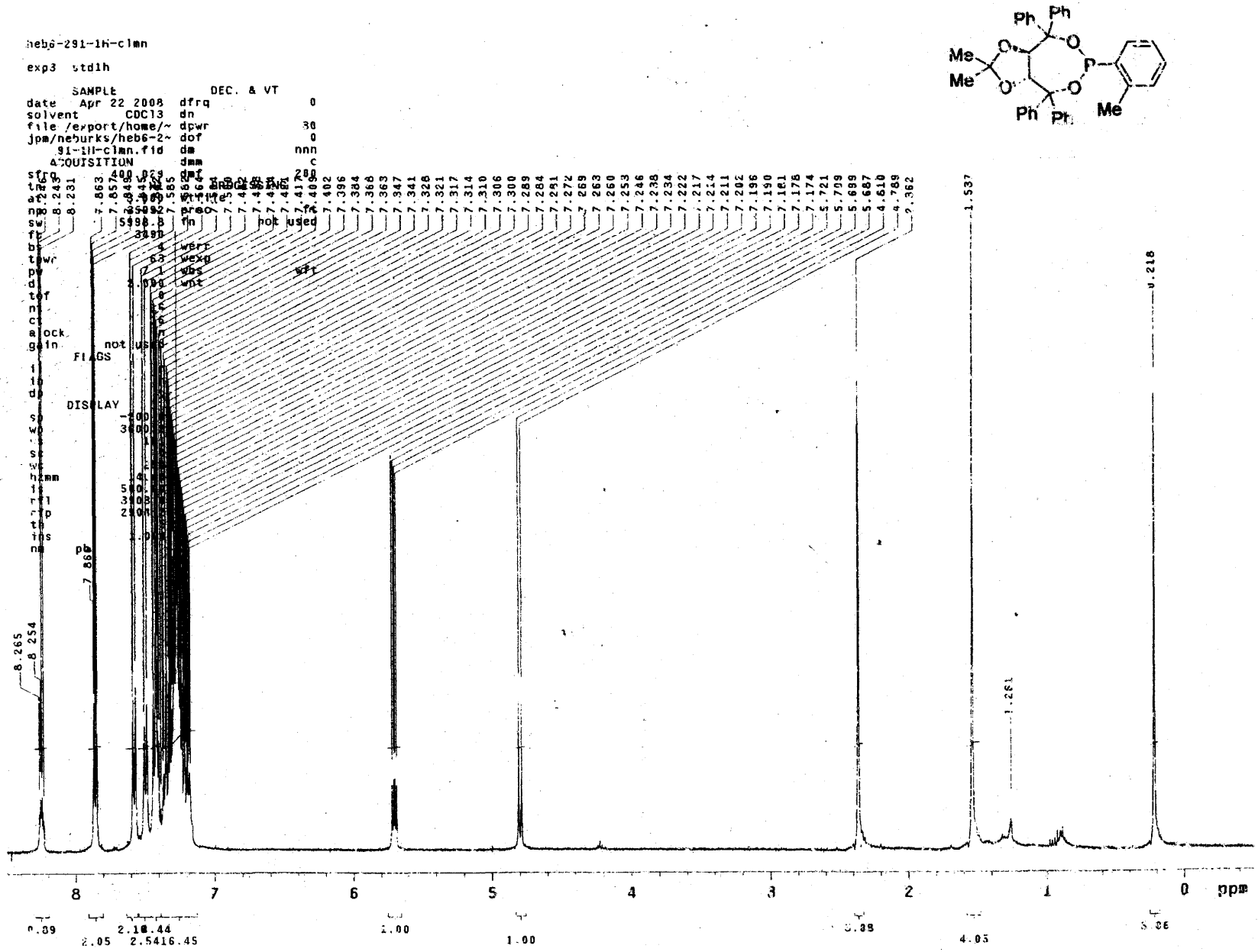
To a separate 100-mL round-bottomed flask with magnetic stir bar was added oven-dried 4Å molecular sieves. The flask was then flame-dried under vacuum and subsequently filled with nitrogen. The flask was charged with TADDOL (1.00 g, 2.16 mmol) and tetrahydrofuran (21 mL, 0.1 M), and triethylamine (1 mL, 7.347 mmol). The flask was cooled to 0 °C (ice/water) and allowed to stir for 15 min at which time the flask was charged with the *ortho*-tolyl dichlorophenylphosphine as a solution in tetrahydrofuran (10 mL). The flask containing the *ortho*-tolyl dichlorophenylphosphine was rinsed twice with tetrahydrofuran (5 mL x 2). The reaction mixture was gradually

warmed to room temperature and allowed to stir overnight. Diethyl ether was added to the reaction mixture to precipitate triethylamine hydrochloride salts which were then removed by filtration over Celite. Solvent was removed by rotary evaporation to afford a foam which was purified by column chromatography on silica gel with 2% ethyl acetate/hexanes as the eluant. A white solid was isolated in 13% yield (165 mg).



(*R,R*)-3.45

(3a*R*,8a*R*)-2,2-Dimethyl-4,4,8,8-tetraphenyl-6-*o*-tolyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine (*R,R*)-3.45. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.21 (3H, s, $(CH_3)_2C$), 1.53 (3H, s, $(CH_3)_2C$), 2.36 (3H, s, CH_3Ar), 4.79 (1H, d, J = 8.4 Hz, CHO), 5.70 (1H, dd, J = 8.8 Hz, J_{HP} = 4.8 Hz, CHO), 7.17-7.36 (11H, m, Ar**H**), 7.39-7.43 (6H, m, Ar**H**), 7.48-7.50 (2H, m, Ar**H**), 7.56-7.58 (2H, m, Ar**H**), 7.84-7.86 (2H, m, Ar**H**), 8.23-8.26 (1H, m, Ar**H**). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5 (d, $^{3}J_{CP}$ = 21.8 Hz), 25.0, 28.0, 82.3 (d, $^{3}J_{CP}$ = 23.4 Hz), 82.5 (d, $^{2}J_{CP}$ = 3.9 Hz), 83.3 (d, $^{2}J_{CP}$ = 7.8 Hz), 83.8 (d, $^{3}J_{CP}$ = 3.9 Hz), 111.4, 127.22, 127.27, 127.3, 127.5, 127.62, 127.68, 127.7, 127.8, 128.1, 128.8 (d, $^{3}J_{CP}$ = 3.1 Hz), 129.3 (d, $^{2}J_{CP}$ = 8.6 Hz), 129.6, 130.4 (d, $^{3}J_{CP}$ = 4.7 Hz), 138.9 (d, $^{1}J_{CP}$ = 14.4 Hz), 141.4 (d, $^{2}J_{CP}$ = 29.6 Hz), 141.6 (d, $^{3}J_{CP}$ = 1.6 Hz), 142.1, 146.2 (d, $^{3}J_{CP}$ = 3.1 Hz), 146.7. ^{31}P NMR (121 MHz, $CDCl_3$) δ 153.4. IR (neat): 3055 (w), 2995 (w), 2918 (w), 2888 (w), 1596 (s), 1491 (s), 798 (s) cm^{-1}. HRMS-(ESI+): for $C_{38}H_{36}O_4P$ calc'd: 587.2351 $(M+H)^+$, observed: 587.2338 $(M+H)^+$. The unpurified reaction mixture was purified on silica gel with 2% ethyl acetate/hexanes as the eluant to afford a white solid in 13% yield (165 mg). R_f = 0.66 (10% ethyl acetate, stain in PMA).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91-1H-clmn.fid
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8
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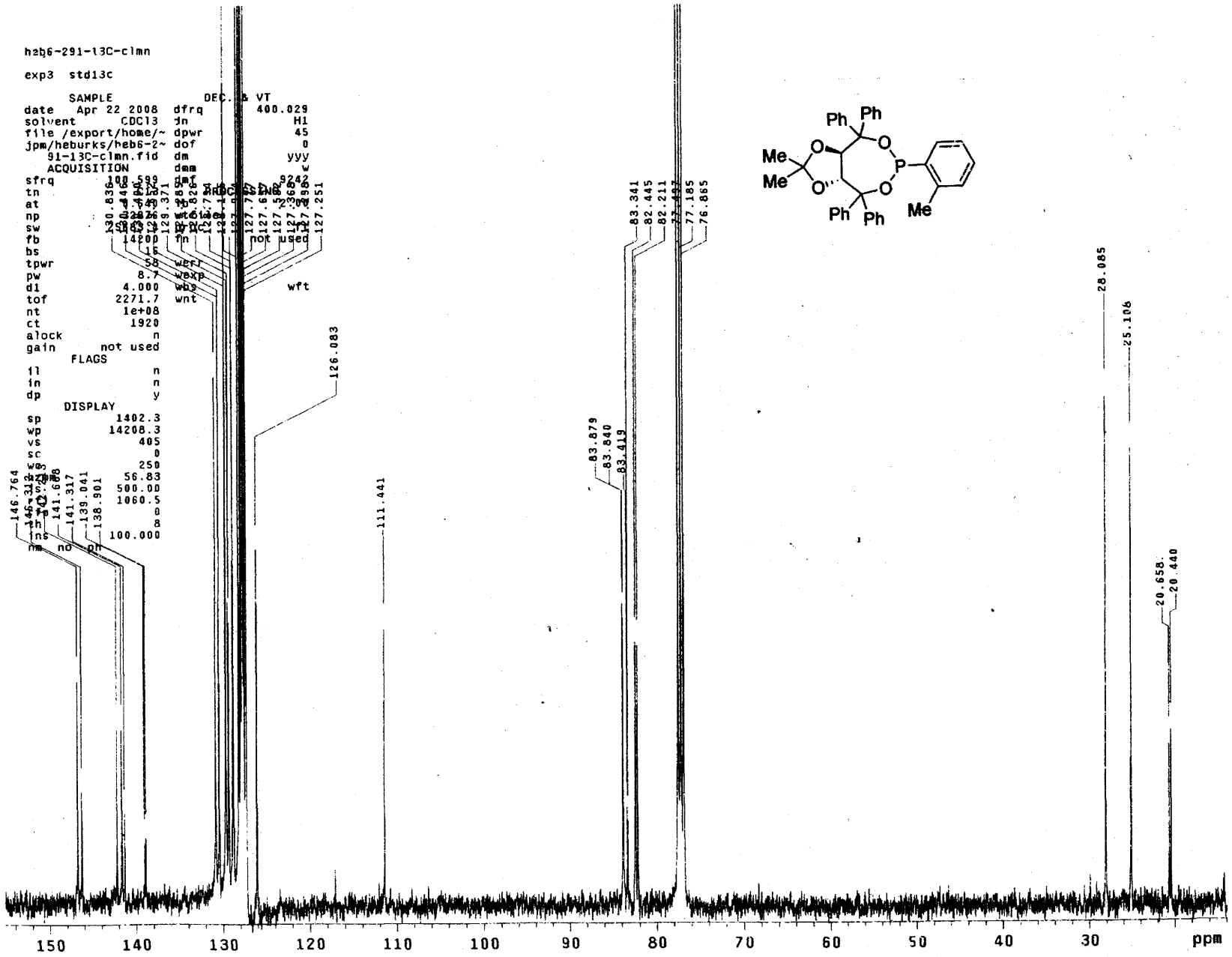
6
5
4
3
2
1
0
ppm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date Apr 22 2008
solvent CDCl3
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91-13C-clmn.fid
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at
np
sw
fb
bs
tpwr
pw
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tof 2271.7
nt 1e+08
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alock n
gain not used
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in n
dp y
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vs 500.00
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dpwr 45
dof 0
dm yyy
dmm w
not used
wft
wnt
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141.688
141.317
139.041
138.901
129.371
127.251
126.083
111.441
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83.341
82.445
82.211
77.185
76.865
28.085
25.106
20.658
20.440
Ph
Ph
O
O
P
Me
Me
O
O
Ph
Ph
Me
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

heb6-291-31P-c1mn

exp1 c2pul

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at	1.280	dres	1.0
np	118108	homo	n
sw	46136.1	PROCESSING	
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bs	8	wtfile	
tpwr	54	proc	ft
pw	5.0	fn	not used
d1	1.000	math	f
tof	4489.5		
nt	64	werr	
ct	64	wexp	
alock	n	wbs	wft
gain	not used	wnt	

FLAGS	
il	n
in	n
dp	y
hs	nn

DISPLAY	
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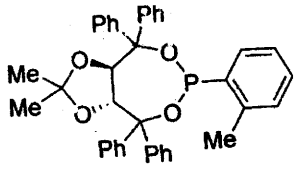
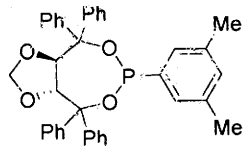
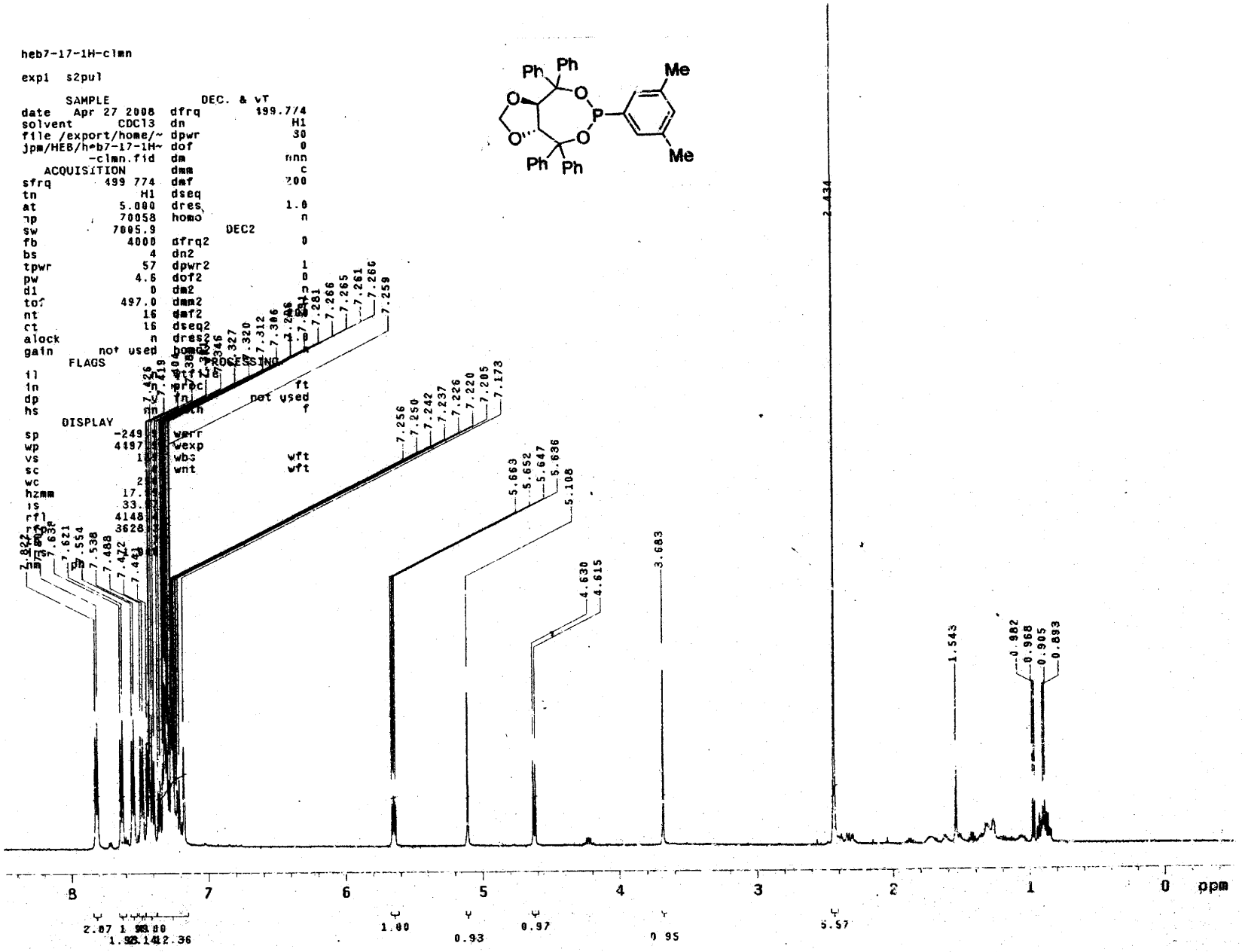
nm no ph





(3a*R*,8a*R*)-6-(3,5-Dimethylphenyl)-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.43 (6H, s, C**H**$_3$Ar), 3.68 (1H, s, OC**H**$_A$H$_B$O), 4.62 (1H, d, J = 7.5 Hz, C**H**O), 5.10 (1H, s, OCH$_A$**H**$_B$O), 5.64 (1H, dd, J = 8 Hz, J_{HP} = 5.5 Hz, C**H**O), 7.17 (1H, s, Ar**H**), 7.20-7.36 (8H, m, Ar**H**), 7.38-7.44 (6H, m, Ar**H**), 7.48 (2H, d, J = 8 Hz, Ar**H**), 7.54 (2H, d, J = 8 Hz, Ar**H**), 7.63 (d, J = 8.5 Hz, Ar**H**), 7.81 (2H, d, J = 7.5 Hz, Ar**H**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 81.0 (d, $^{3}J_{CP}$ = 26.3 Hz), 82.22 (d, $^{2}J_{CP}$ = 3.8 Hz), 82.30 (d, $^{2}J_{CP}$ = 7.12 Hz), 85 32 (d, $^{3}J_{CP}$ = 4.4 Hz), 95.9, 127.3, 127.4, 127.50, 127.55, 127.72, 127.76, 127.9, 128.14, 128.19, 128.2, 128.42 (d, $^{2}J_{CP}$ = 20.25 Hz), 128.44, 132.7, 138.1 (d, $^{3}J_{CP}$ = 8.75 Hz), 140.2, 140.6 (d, $^{1}J_{CP}$ = 9.8 Hz), 141.4, 145.1, 146.1. ^{31}P NMR (121 MHz, $CDCl_3$) δ 159.4. IR (neat). 3061 (w), 2921 (w), 2869 (w), 2249 (w), 1447 (m), 904 (s), 724 (s), 648 (s) cm^{-1}. HRMS-(ESI+): for $C_{37}H_{34}O_4P$ calc'd: 573.2195 $(M+H)^+$, observed: 573.2188 $(M+H)^+$. The unpurified reaction mixture was purified on silica gel with 2% ethyl acetate/hexanes as the eluant to afford a white solid in 14% yield (172 mg). R_f = 0.41 (10% ethyl acetate, stain in PMA).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bs 4
tpwr 57
pw 4.6
d1 0
to 497.0
nt 16
ct 16
alock n
gain not used
FLAGS
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dm nnn
dmm c
dmf 200
dseq
dres 1.0
homo n
DEC2
dfrq2 0
dn2
dpwr2 1
dof2 0
dm2
dmm2
dmf2
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homo
PROCESSING
wft
wft
Ph
Ph
Ph
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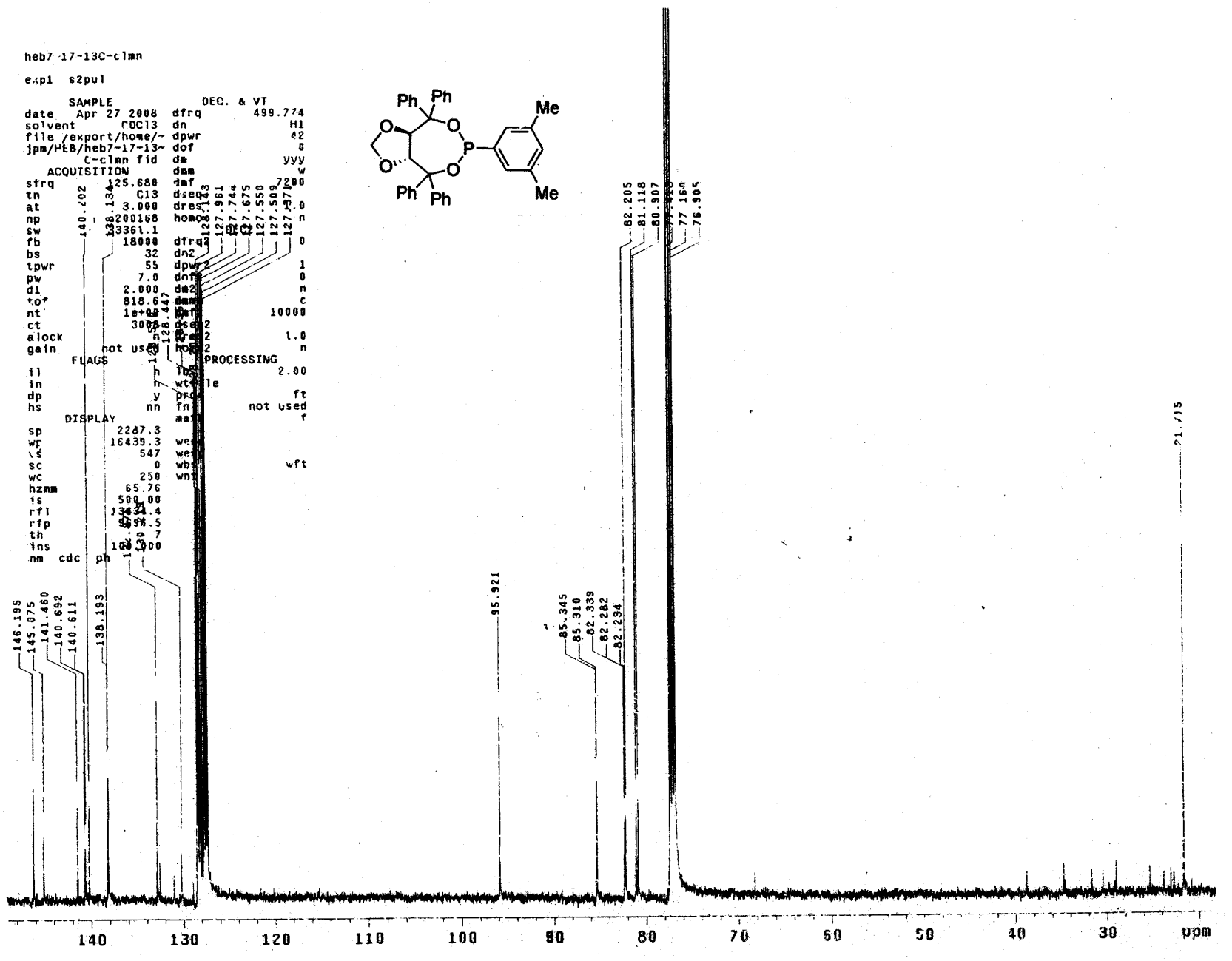
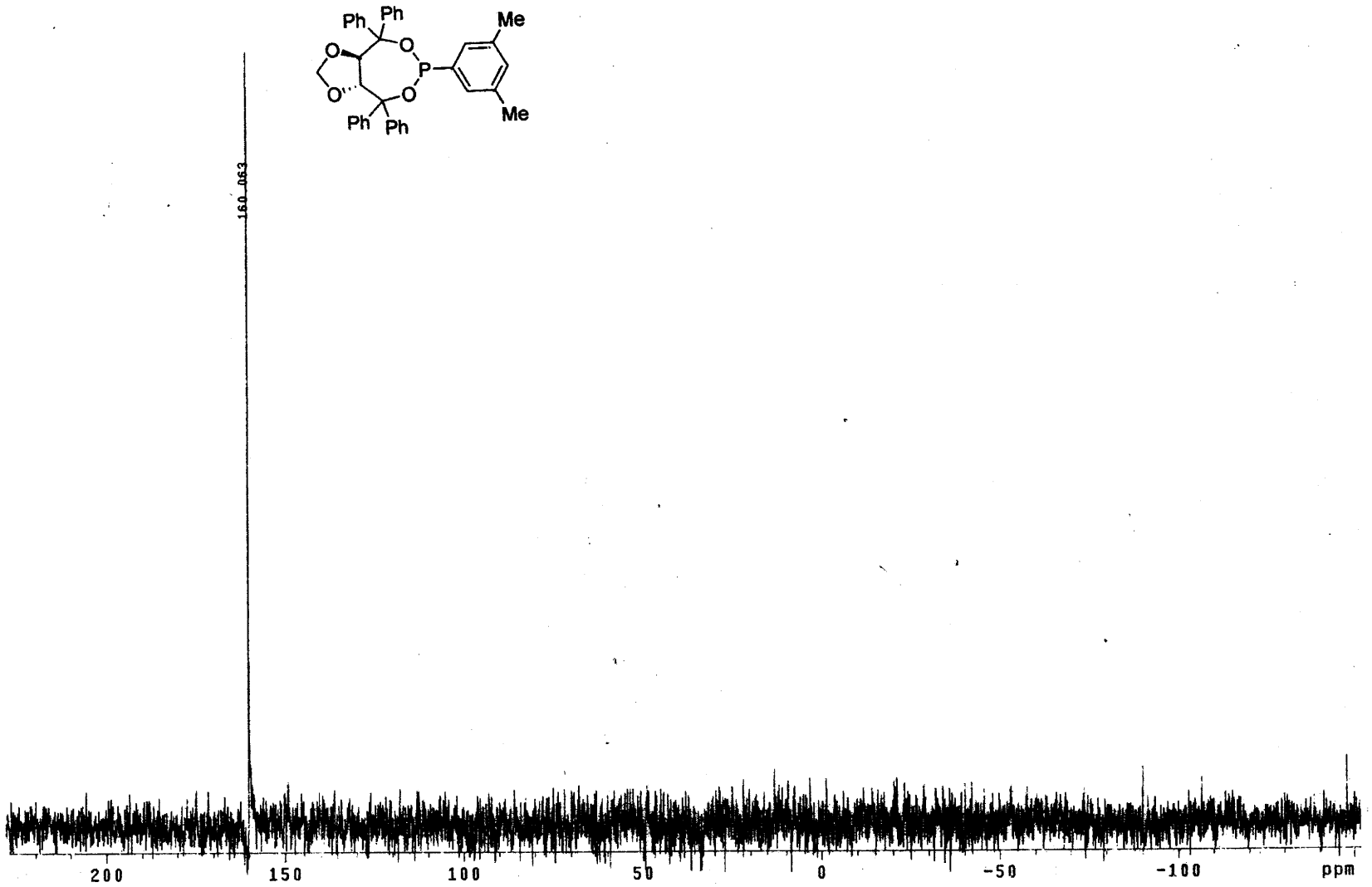
5.652
5.647
5.636
5.108
4.630
4.615
3.683
2.434
1.543
0.982
0.968
0.905
0.893
8
7
6
5
4
3
2
1
0
ppm
2.87
1.00
0.93
0.97
0.95
5.57


heb7-17-13C-clmn
exp1 s2pul
SAMPLE
date Apr 27 2008
solvent CDCl3
file /export/home/~
jpm/HEB/heb7-17-13~
C-clmn fid
ACQUISITION
sfrq 125.680
tn C13
at 3.000
np 200168
sw 33361.1
fb 18000
bs 32
tpwr 55
pw 7.0
d1 2.000
to 818.6
nt 1e+06
ct 3008
alock
gain not used
FLAGS
il
in
dp y
hs nn
DISPLAY
sp 2287.3
wp 16439.3
vs 547
sc 0
wc 250
hzmm 65.76
is 500.00
rfl 3
rfp 6
th 7
ins 1
nm cdc ph
DEC. & VT
dfrq 499.774
dn H1
dpwr 42
dof 0
dm yyy
dmm w
dmf 7200
dseq
dres 1.3
homo
dfrq2
dn2
dpwr2 1
dof2 0
dm2 n
dmm2 c
dmf2 10000
dseq2
dres2
homo2
dfrq2 1.0
dn2 n
PROCESSING
lb 2.00
wtfile
fn not used
mat f
wef
wexp
wbs wft
wnt
Ph
Ph
O
O
P
Me
Me
O
O
Ph
Ph
146.195
145.075
141.460
140.692
140.611
138.193
95.921
85.345
85.310
82.339
82.282
82.234
82.205
81.118
80.907
77.160
76.905
21.715
140
130
120
110
100
90
80
70
60
50
40
30
ppm


Ph
Ph
Me
O
O
P
O
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Ph
Ph
Me
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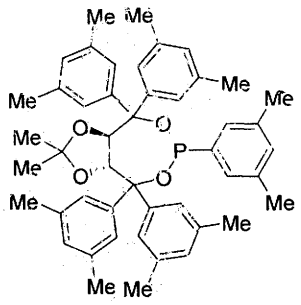
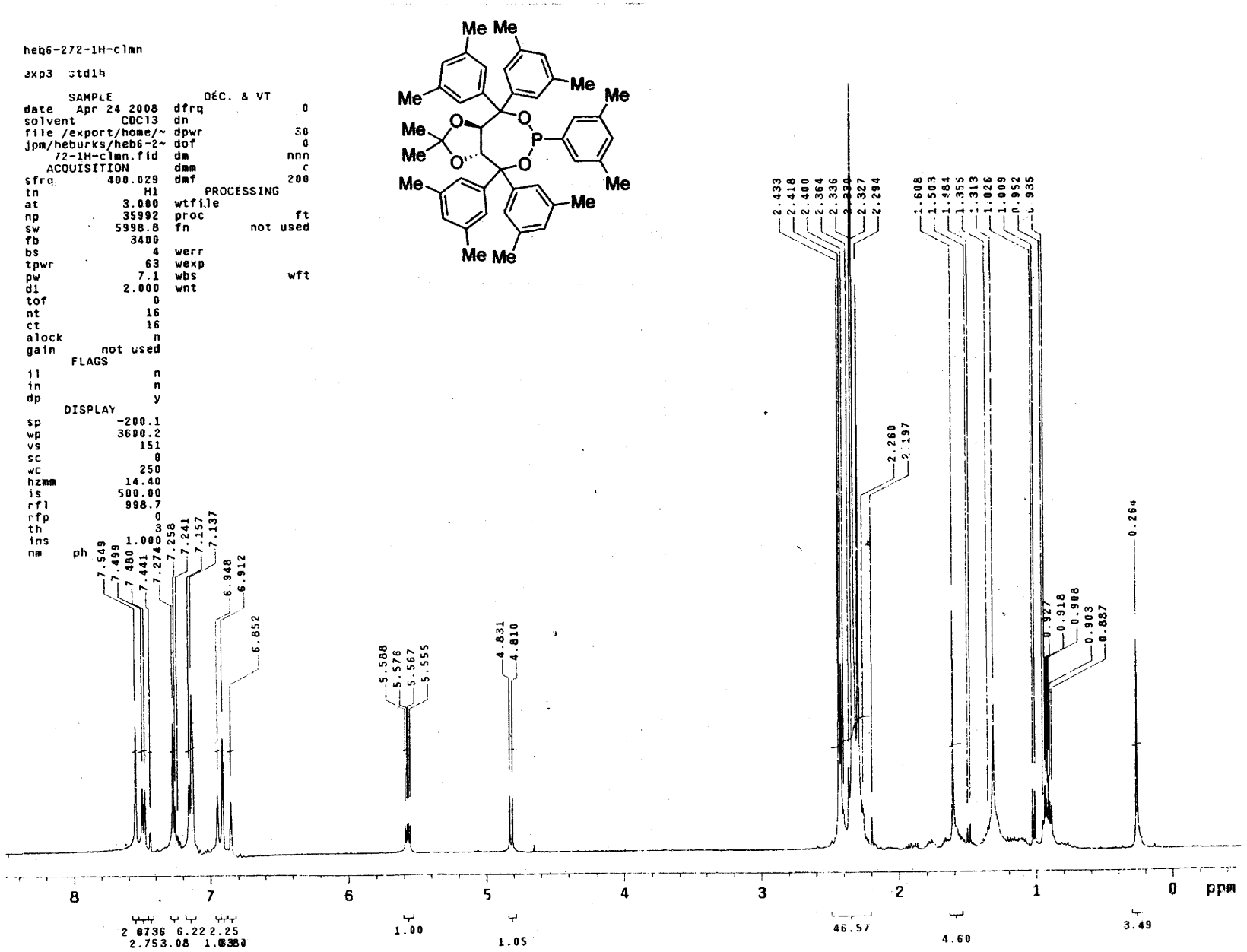
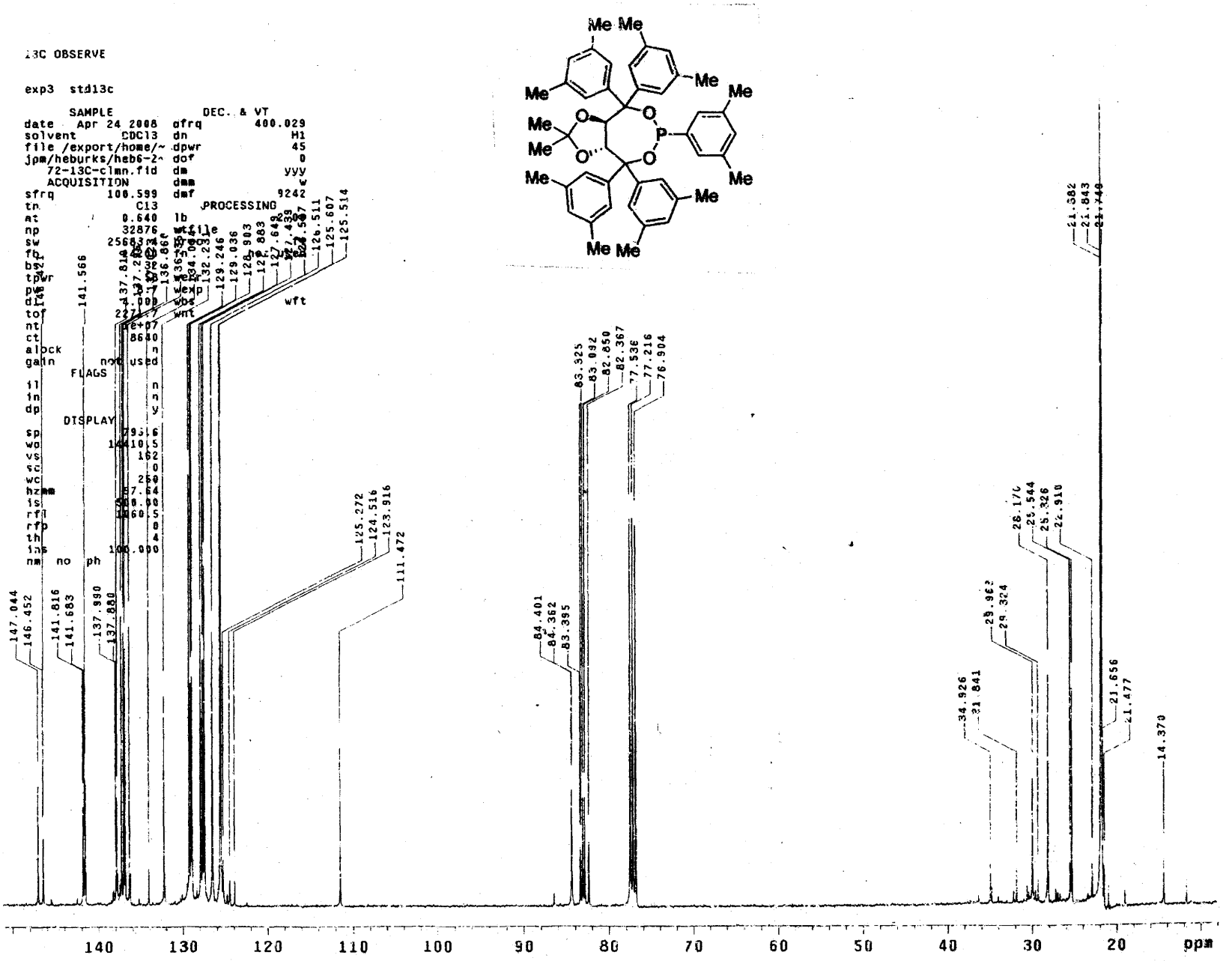
200
150
100
50
0
-50
-100
ppm



(*R,R*)-3.44

(3a*R*,8a*R*)-4,4,6,8,8-Pentakis(3,5-dimethylphenyl)-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine (*R,R*)-3.44. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.26 (3H, s, $(CH_3)_2C$), 1.60 (3H, s, $(CH_3)_2C$), 2.29-2.40 (30H, m, CH_3Ar), 4.82 (1H, d, J = 8.4 Hz, CHO), 5.57 (1H, dd, J = 8.4 Hz, J_{HP} = 4.8 Hz, CHO), 6.85 (1H, s, Ar**H**), 6.91 (2H, s, Ar**H**), 6.94 (1H, s, Ar**H**), 7.13-7.15 (5H, m, Ar**H**), 7.48 (1H, s, Ar**H**), 7.49 (1H, s, Ar**H**), 7.54 (2H, s, Ar**H**). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 21.7, 21.8, 25.2, 28.1, 29.9, 82.3, 82.9 (d, $^3J_{CP}$ = 24.2Hz), 83.3 (d, $^2J_{CP}$ = 7.0 Hz), 84.3 (d, $^3J_{CP}$ = 3.9 Hz), 111.4, 125.4, 125.5, 126.4, 127.3, 127.5, 127.8, 128.9 (d, $^2J_{CP}$ = 13.3 Hz), 129.1, 132.1, 136.2, 136.8, 136.9, 137.2, 137.8 (d, $^2J_{CP}$ = 7.0 Hz), 141.51, 141.56 (d, $^1J_{CP}$ = 11.7 Hz), 141.7, 146.3 (d, $^3J_{CP}$ = 3.9 Hz), 146.9. ^{31}P NMR (121 MHz, $CDCl_3$) δ 157.2. IR (neat): 2915 (m), 2854 (m), 1600 (m), 1457 (m), 1158 (m), 883 (m) cm^{-1}. HRMS-(ESI+): for $C_{47}H_{54}O_4P$ calc'd: 713.3760 $(M+H)^+$, observed: 713.3773 $(M+H)^+$. The unpurified reaction mixture was purified on silica gel with 2% ethyl acetate/hexanes as the eluant to afford a white solid in 7% yield (112.8 mg). R_f = 0.51 (10% ethyl acetate, stain in PMA).


heb6-272-1H-clmn
exp3 std1h
SAMPLE
date Apr 24 2008
solvent CDCl3
file /export/home/~
jpm/heburks/heb6-2~
72-1H-clmn.fid
ACQUISITION
sfrq 400.029
tn H1
at 3.000
np 35992
sw 5998.8
fb 3400
bs 4
tpwr 63
pw 7.1
d1 2.000
tof 0
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -200.1
wp 3600.2
vs 151
sc 0
wc 250
hzmm 14.40
is 500.00
rfl 998.7
rfp 0
th 3
ins 1.000
nm ph
DEC. & VT
dfrq 0
dn
dpwr 38
dof 0
dm nnn
dmm c
dmf 200
PROCESSING
wtfile
proc ft
fn not used
werr
wexp
wbs wft
wnt
Me
O
P
7.549
7.499
7.480
7.441
7.274
7.258
7.241
7.157
7.137
6.948
6.912
6.852
5.588
5.576
5.567
5.555
4.831
4.810
2.433
2.418
2.400
2.364
2.336
2.327
2.294
2.260
2.197
1.608
1.503
1.484
1.355
1.313
1.026
1.009
0.952
0.935
0.927
0.918
0.908
0.903
0.887
0.264
8
7
6
5
4
3
2
1
0
ppm
2.75
3.08
1.00
1.05
46.57
4.60
3.49


13C OBSERVE
exp3 std13c
SAMPLE
date Apr 24 2008
solvent CDCl3
file /export/home/~
jpm/heburks/heb6-2^
72-13C-clmn.fid
ACQUISITION
sfrq 100.599
tn C13
at 0.640
np 32876
sw 25641.0
fb 40000
bs 32
tdpwr 50
pw 9.7
d1 1.000
tof 2271.7
nt 1e+07
ct 8640
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -3516
wp 14410.5
vs 162
sc 0
wc 250
hzmm 57.64
is 0.00
rfl 160.5
rfp 0
th 4
ins 100.000
nm no ph
DEC. & VT
dfrq 400.029
dn H1
dpwr 45
dof 0
dm yyy
dmm c
dmf 9242
PROCESSING
lb
wtfile
sb 0.00
sbs 0.000
wexp
wbs
wnt
wft
Me
O
P
147.044
146.452
141.816
141.683
137.990
137.880
125.272
124.516
123.916
111.472
84.401
84.362
83.395
83.325
83.092
82.850
82.367
77.538
77.216
76.904
34.926
31.841
29.962
29.324
28.176
25.544
25.326
24.910
21.656
21.477
14.370
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

```
heb6-272-31p

exp1  s2pul

      SAMPLE
date    Apr 24 2008
solvent       CDCl3
file  /export/home/~
jpm/heburks/heb6-2~
         72-31p.fid
   ACQUISITION
sfrq        121.423
tn              P31
at            1.280
np          118108
sw          46136.1
fb            25400
bs                4
tpwr             54
pw              5.0
d1            1.000
tof          4489.5
nt               16
ct                8
alock             n
gain      not used
      FLAGS
il                n
in                n
dp                y
ns               nn
      DISPLAY
sp          -1148.1
wp          28857.3
vs              104
sc                0
wc              250
hzmm         115.43
is           354.40
rfl         18426.1
rfp               0
th               65
ins          100.000
nm  no  ph

      DEC. & VT
dfrq        299.941
dn               H1
dpwr             48
dof               0
dm              yyy
dmm               w
dmf            9900
dseq
dres            1.0
homo              n
     PROCESSING
lb             2.00
wtfile
proc             ft
fn         not used
math              f
werr
wexp
wbs             wft
wnt
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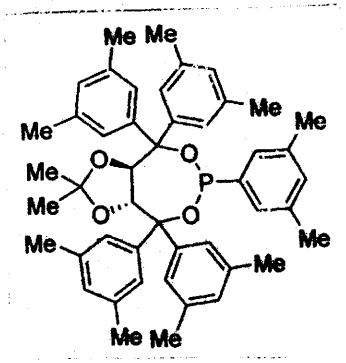
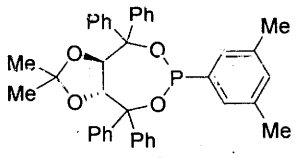
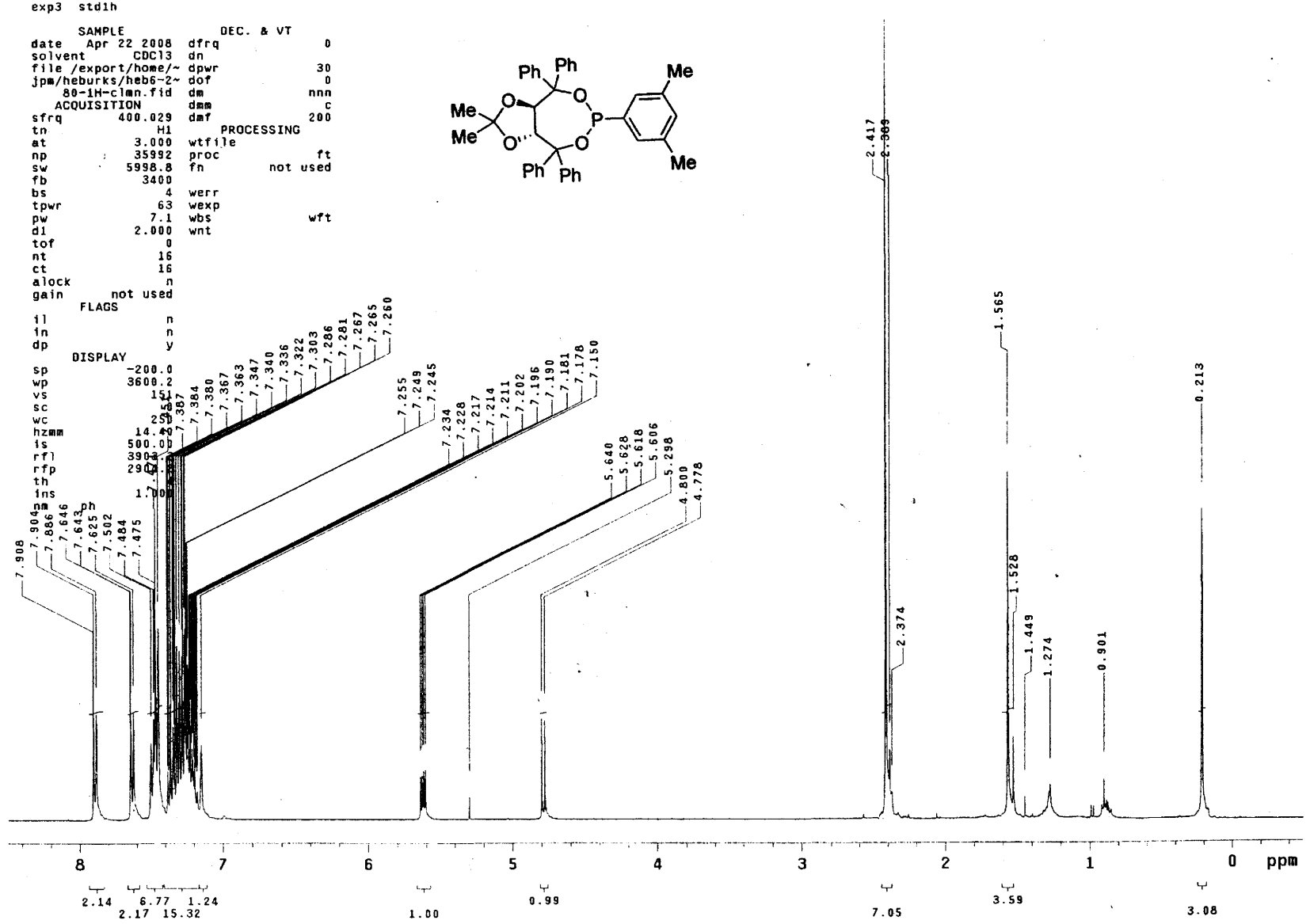




(*R,R*)-3.43

(3a*R*,8a*R*)-6-(3,5-Dimethylphenyl)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine (*R,R*)-3.43. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.21 (3H, s, $(CH_3)_2C$), 1.56 (3H, s, $(CH_3)_2C$), 2.41 (6H, s, CH_3Ar), 4.78 (1H, d, J = 8.8 Hz, CHO), 5.62 (1H, dd, J = 8.8 Hz, J_{HP} = 4.8 Hz, CHO), 7.15 (1H, s, ArH), 7.19-7.38 (12H, m, ArH), 7.45-7.50 (6H, m, ArH), 7.62-7.64 (2H, m, ArH), 7.88-7.90 (2H, m, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 24.9, 28.0, 82.2, 82.7 (d, $^{3}J_{CP}$ = 23.4 Hz), 83.3 (d, $^{2}J_{CP}$ = 7.7 Hz), 84.1 (d, $^{3}J_{CP}$ = 3.8 Hz), 111.4, 127.21, 127.26, 127.3, 127.4, 127.5, 127.6, 127.7, 128.1 (d, $^{2}J_{CP}$ = 17.2 Hz), 128.6, 128.7, 129.5, 132.6, 137.9 (d, $^{2}J_{CP}$ = 7.8 Hz), 140.9 (d, $^{1}J_{CP}$ = 10.9 Hz), 141.5, 142.0, 146.0, 146.9. ^{31}P NMR (121 MHz, $CDCl_3$) δ 158.0. IR (neat): 3057 (w), 3001 (w), 2914 (w), 1600 (s), 1046 (s), 872 (s) cm^{-1}. HRMS-(ESI+): for $C_{39}H_{38}O_4P$ calc'd: 601.2479 $(M+H)^+$, observed: 601.2508 $(M+H)^+$. The unpurified reaction mixture was purified on silica gel with 2% ethyl acetate/hexanes as the eluant to afford a white solid in 26% yield (344.6 mg). R_f = 0.59 (10% ethyl acetate, stain in PMA).


heb6-280-1H-clmn
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date Apr 22 2008
solvent CDCl3
file /export/home/~
jpm/heburks/heb6-2~
80-1H-clmn.fid
ACQUISITION
sfrq 400.029
tn H1
at 3.000
np 35992
sw 5998.8
fb 3400
bs 4
tpwr 63
pw 7.1
d1 2.000
tof 0
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -200.0
wp 3600.2
vs 15
DEC. & VT
dfrq 0
dn
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
PROCESSING
wtfile
proc ft
fn not used
werr
wexp
wbs wft
wnt
Ph
Ph
Me
Me
O
O
O
O
P
Me
Ph
Ph
Me
7.908
7.904
7.886
7.646
7.643
7.625
7.502
7.484
7.475
7.387
7.384
7.380
7.367
7.363
7.347
7.340
7.336
7.322
7.303
7.286
7.281
7.267
7.265
7.260
7.255
7.249
7.245
7.234
7.228
7.217
7.214
7.211
7.202
7.196
7.190
7.181
7.178
7.150
5.640
5.628
5.618
5.606
5.298
4.800
4.778
2.417
2.374
1.565
1.528
1.449
1.274
0.901
0.213
8
7
6
5
4
3
2
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1.00
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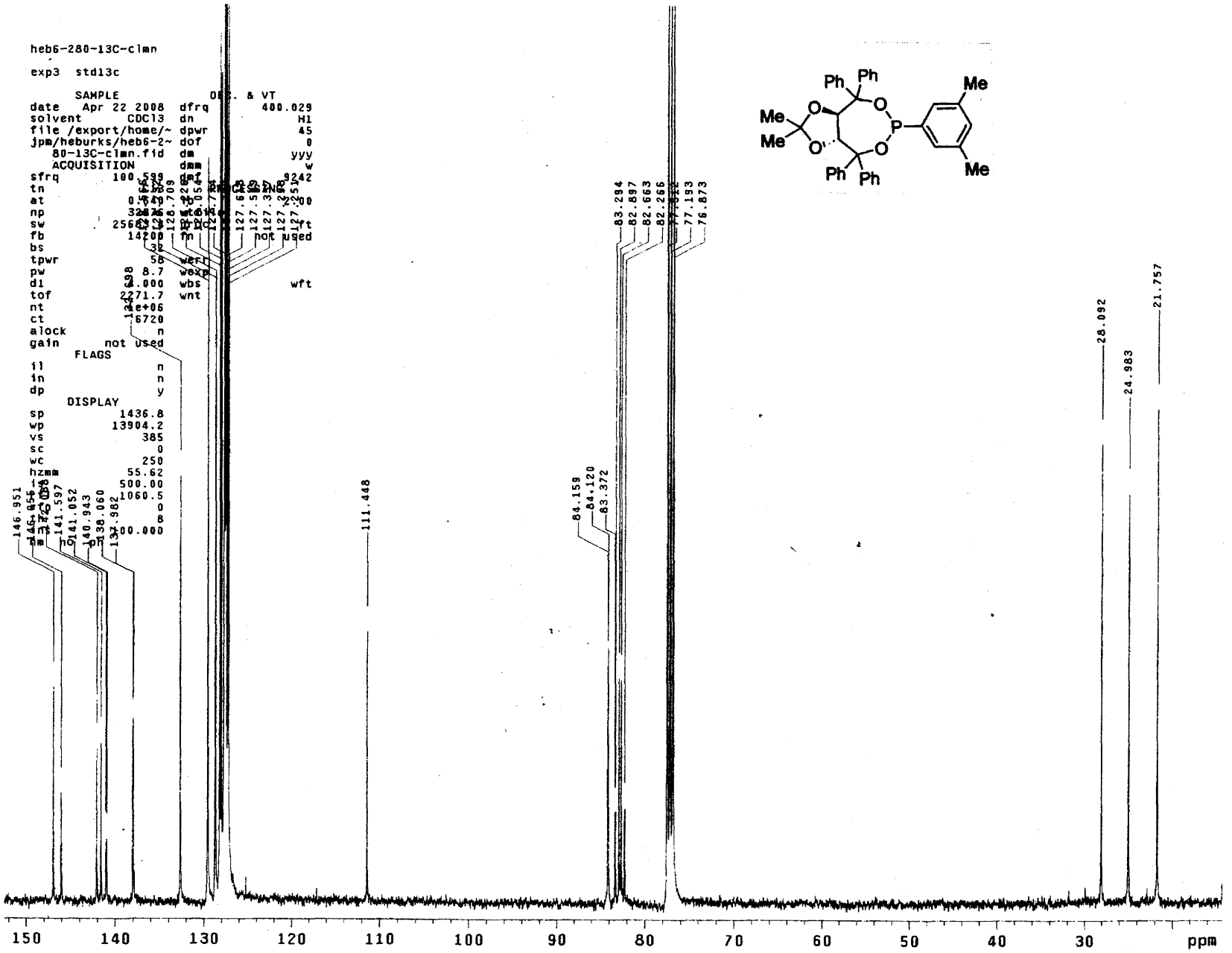
3.59
3.08


heb6-280-13C-clmn
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date Apr 22 2008
solvent CDCl3
file /export/home/~
jpm/heburks/heb6-2~
80-13C-clmn.fid
ACQUISITION
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np 32
sw 25662.1
fb 14200
bs 32
tpwr 56
pw 8.7
dl 2.000
tof 2271.7
nt 1e+06
ct 16720
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp 1436.8
wp 13904.2
vs 385
sc 0
wc 250
hzmm 55.62
500.00
1060.5
0
8
100.000
DEC. & VT
dfrq 400.029
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dpwr 45
dof 0
dm yyy
dmm w
dmf 9242
tn H1
at 2.00
np 32
sw 6410.3
fb not used
bs
tpwr
pw
dl
tof
nt
ct
alock
gain
wft
wft
146.951
141.597
141.052
140.943
138.060
137.982
128.709
127.681
127.553
127.386
127.285
127.200
111.448
84.159
84.120
83.372
83.294
82.897
82.663
82.266
77.193
76.873
28.092
24.983
21.757
Ph
Ph
Me
Me
O
O
P
Me
Me
O
O
Ph
Ph
Me
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

heb6-280-31p-clmn

exp1 s2pul

SAMPLE		DEC. & VT	
date	Jan 19 2008	dfrq	299.948
solvent	CDCl3	dn	H1
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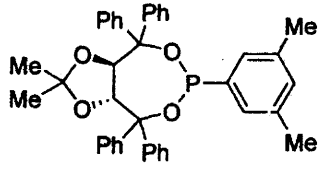
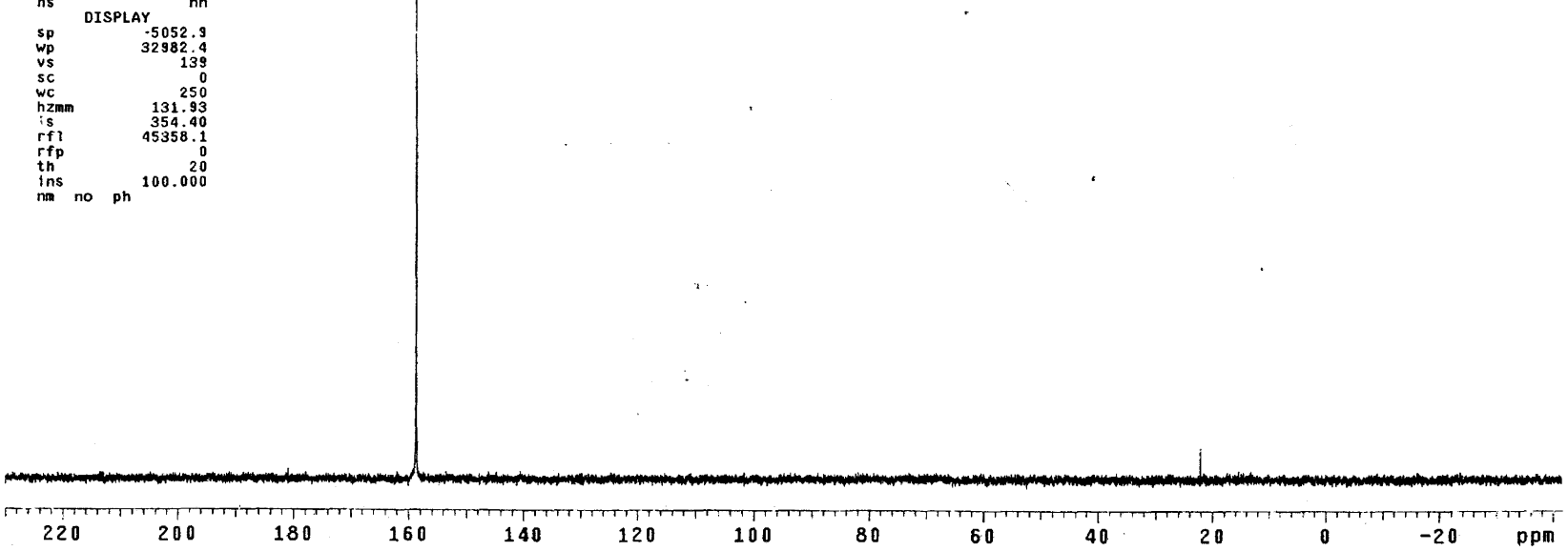
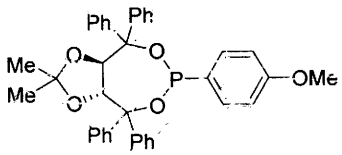
	jpm/heburks/heb6-2~	dof	0
	80-31p-clmn.fid	dm	yyy
ACQUISITION		dmm	w
sfrq	121.425	dmf	9900
tn	P31	dseq	
at	0.640	dres	1.0
np	128000	homo	n
sw	100000.0	PROCESSING	
fb	49500	lb	2.00
bs	8	wtfile	
tpwr	54	proc	ft
pw	5.0	fn	not used
d1	1.000	math	f
tof	4489.5		
nt	64	werr	
ct	32	wexp	
alock	n	wbs	wft
gain	not used	wnt	
FLAGS			
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-5052.9		
wp	32982.4		
vs	139		
sc	0		
wc	250		
hzmm	131.93		
is	354.40		
rfl	45358.1		
rfp	0		
th	20		
ins	100.000		
nm no ph			

158.654

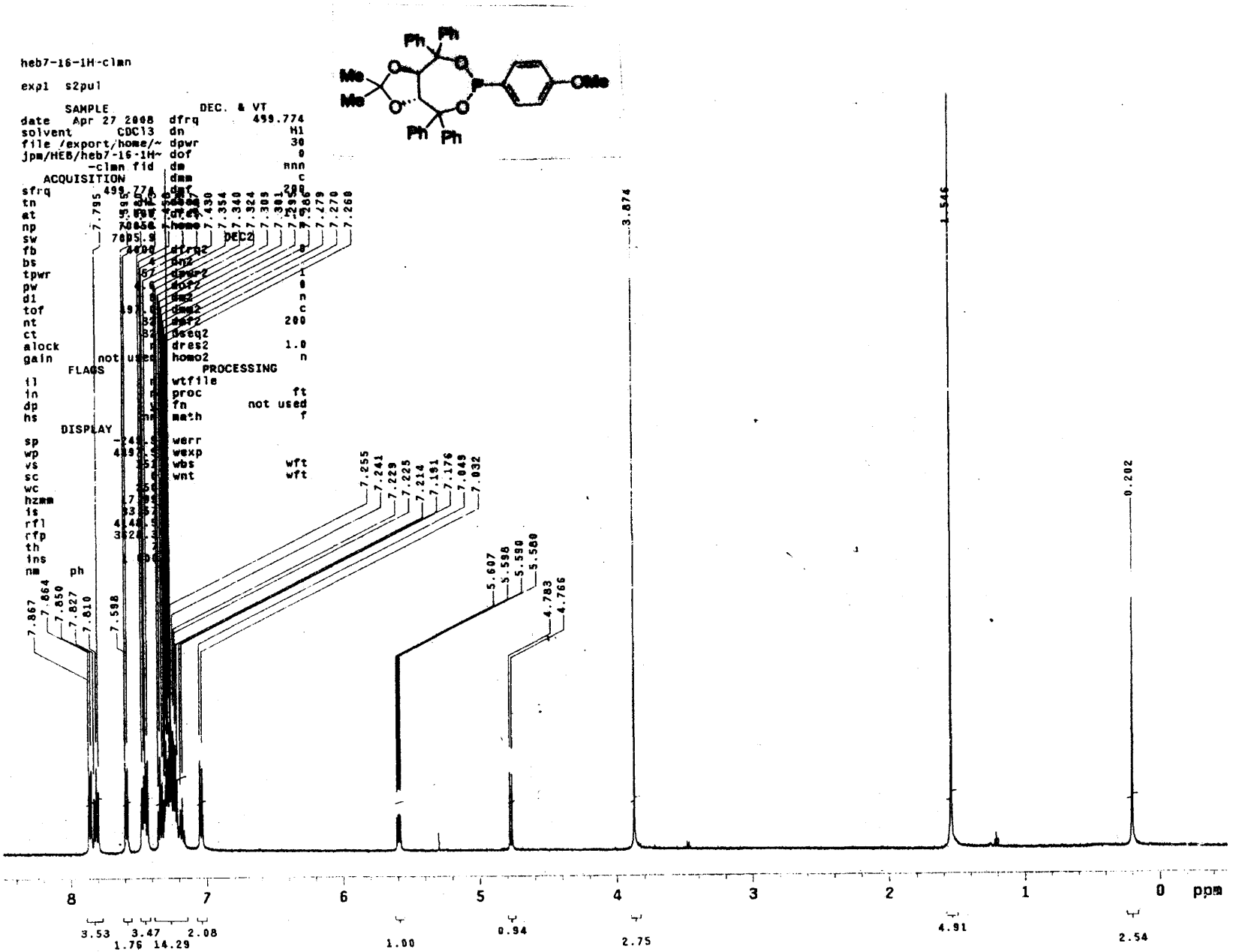






(*R,R*)-3.45

(3a*R*,8a*R*)-6-(4-Methoxyphenyl)-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine (*R,R*)-3.45. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.20 (3H, s, $(CH_3)_2C$), 1.54 (3H, s, $(CH_3)_2C$), 3.87 (3H, s CH_3OAr), 4.77 (1H, J = 8.5 Hz, CHO), 5.59 (1H, dd, J = 8.5 Hz, J_{HP} = 4.5 Hz, CHO), 7.04 (2H, d, J = 8.5 Hz, ArH), 7.16-7.35 (12H, m, ArH), 7.43-7.47 (4H, m, ArH), 7.58 (2H, d, J = 7.5 Hz, ArH), 7.81 (2H, t, J = 7.5 Hz, ArH), 7.86 (2H, d, J = 7 Hz, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 55.4, 82.1 (d, $^{2}J_{CP}$ = 3.4 Hz), 82.7 (d, $^{3}J_{CP}$ = 18.4 Hz), 83.1 (d, $^{2}J_{CP}$ = 6.1 Hz), 84.0 (d, $^{3}J_{CP}$ = 3.2 Hz), 111.1, 114.2 (d, $^{3}J_{CP}$ = 6.7 Hz), 127.2, 127.31, 127.34, 127.4, 127.5, 127.6, 127.73, 127.75, 128.0, 128.2, 128.7, 128.8, 129.4, 131.8 (d, $^{2}J_{CP}$ = 20.8 Hz), 132.7 (d, $^{1}J_{CP}$ = 12 Hz), 141.5, 142.1, 146.0, 147.0, 161.9. ^{31}P NMR (121 MHz, $CDCl_3$) δ 157.2. IR (neat): 3059 (m), 3024 (m), 2991 (m), 2933 (m), 1736 (s), 1498 (s), 1405 (s), 1215 (s), 1112 (s), 699 (s) cm^{-1}. HRMS-(ESI+): for $C_{38}H_{35}O_4NaP$ calc'd: 625.2120 $(M+Na)^+$, observed: 625.2116 $(M+Na)^+$. The unpurified reaction mixture was purified on silica gel with 2% ethyl acetate/hexanes as the eluant to afford a white solid in 5% yield (62 mg). R_f = 0.37 (10% ethyl acetate, stain in PMA).


heb7-16-1H-clmn
expl s2pul
SAMPLE
date Apr 27 2008
solvent CDCl3
file /export/home/~
jpm/HEB/heb7-16-1H~
-clmn fid
ACQUISITION
sfrq 499.774
tn H1
at 3.99
np 78858
sw 7895.9
fb 4400
bs 4
tpwr 57
pw 6.5
d1 1.000
tof 899.9
nt 8
ct 8
alock n
gain not used
FLAGS
il n
in n
dp y
hs nn
DISPLAY
sp -244.1
wp 4497.1
vs 10
sc 0
wc 250
hzmm 17.96
is 33
rfl 4144.5
rfp 3524.5
th 0
ins 1
nm ph
DEC. & VT
dfrq 499.774
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
dm2 n
dmm2 c
dmf2 200
dseq2
dres2 1.0
homo2 n
PROCESSING
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math f
werr
wexp
wbs wft
wnt wft
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Ph
Me
Me
OMe
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6
5
4
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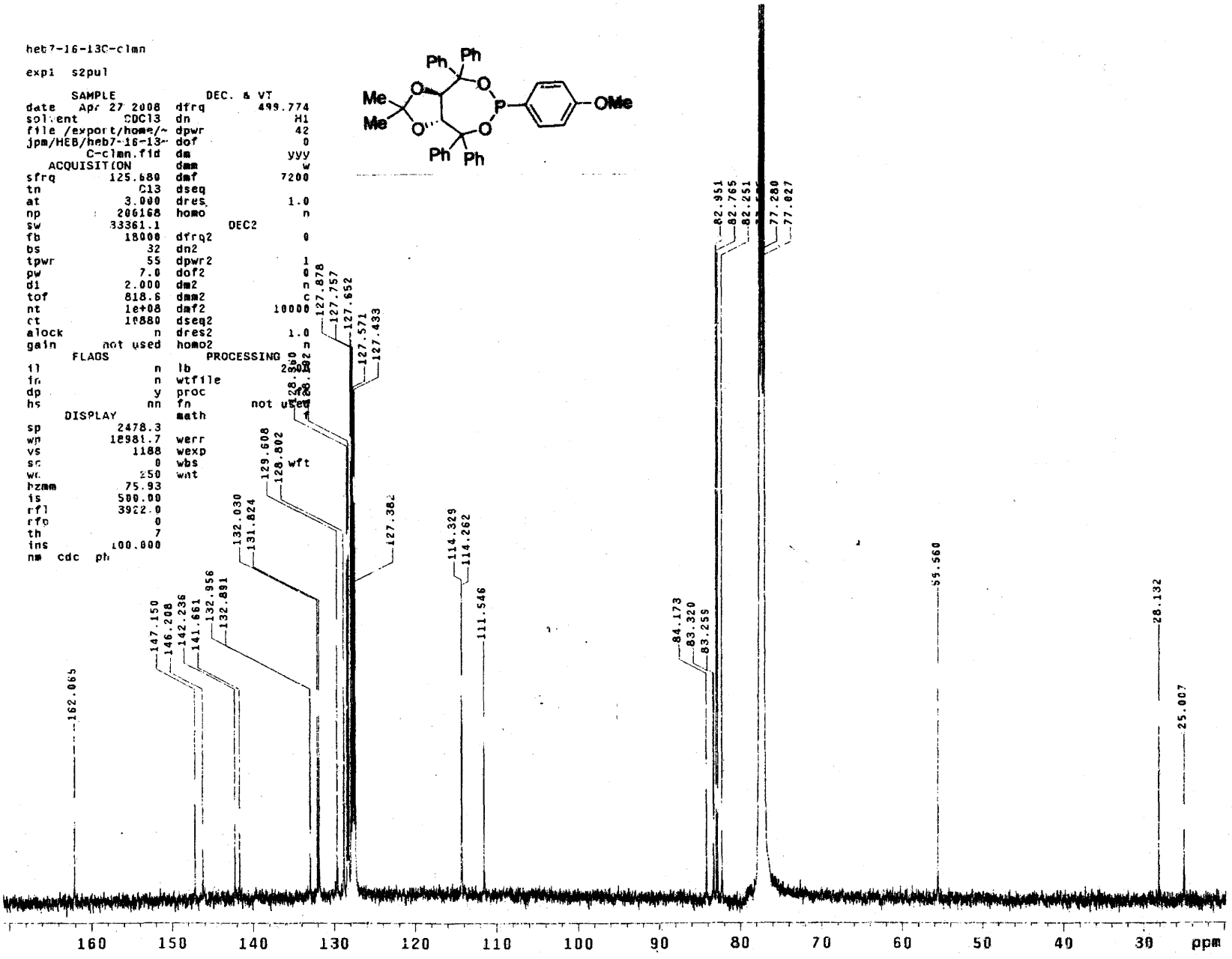
2.75
4.91
2.54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date Apr 27 2008
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30
ppm

heb7-16-13P-clmn

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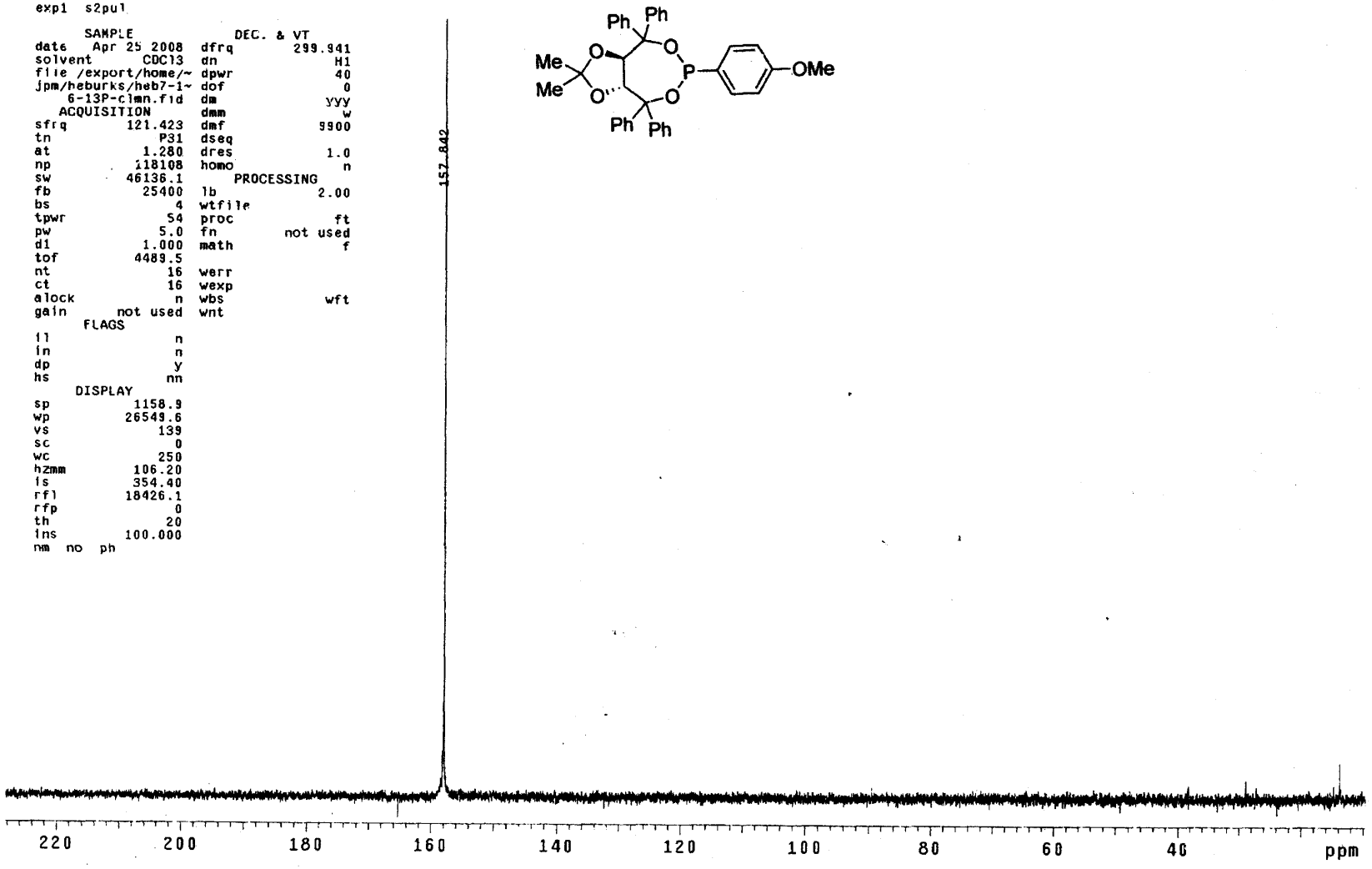
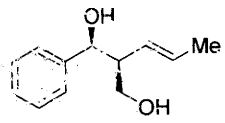


3.5.5. General Procedure for Diene Diboration/Allylation/Oxidation.

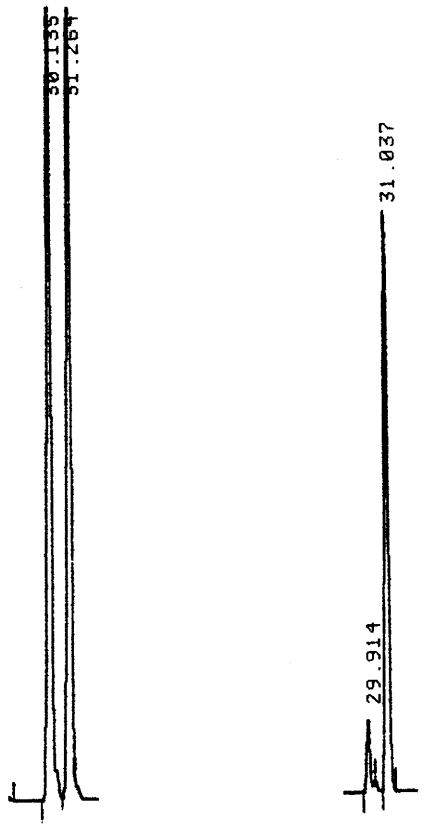
In a dry box, a 6-dram vial with magnetic stir bar was charged with $Pt_2(dba)_3$ (8 mg, 7.3 μmol), (*R,R*)-xylylTADDOLPPh **(*R,R*)-3.33** (12 mg, 0.017 mmol), and toluene (2.9 mL, 0.1 M). After stirring for 1 h, $B_2(pin)_2$ (78 mg, 0.31 mmol) was added to the mixture followed by *trans*-piperylene (22 mg, 0.29 mmol). The vial was sealed with a polypropylene cap, removed from dry box, and stirred at 60 °C for 14 h. The reaction mixture was cooled to ambient temperature and charged with freshly washed (10% sodium carbonate followed by sodium sulfite) and distilled benzaldehyde (35 μL, 0.35 mmol). The reaction was allowed to stir at room temperature for 24 h at which time the reaction mixture was cooled to 0 °C (ice/water) and charged with tetrahydrofuran (3 mL), 3 M sodium hydroxide (2 mL), and 30% hydrogen peroxide (1 mL). The reaction was gradually warmed to room temperature and allowed to stir for 12 h at which time the vial was cooled to 0 °C (ice/water). Saturated sodium thiosulfate was added dropwise over 5 min, the reaction mixture was diluted with ethyl acetate and transferred to a separatory funnel. The aqueous and organic layers were separated, the aqueous layer was rinsed three times with ethyl acetate. The organic extracts were combined and washed with brine. The organic layer was dried (Na_2SO_4), filtered, and volatiles were removed by rotary evaporation. The unpurified reaction mixture was purified on silica gel with 50% ethyl acetate/hexanes as the eluant to afford a white solid in 82% yield (52 mg).



(1*S*,2*S*)-1-Phenyl-2-((*E*)-prop-1-enyl)propane-1,3-diol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48-1.59 (3H, m, $\mathbf{CH_3}$), 2.38 (1H, t, J = 5.6 Hz, **OH**), 2.50 (1H, p, J = 6.9 Hz, $\mathbf{CH}CH_2OH$), 2.64 (1H, br s, **OH**), 3.63 (1H, dd, J = 10.8, 5.4 Hz, $HOCH_A\mathbf{H_B}$), 3.71 (1H, dd, J = 10.8, 5.7 Hz, $HOCH_A\mathbf{H_B}$), 4.66 (1H, dd, J = 7.4, 3.4 Hz, $PhC\mathbf{H}OH$), 5.14 (1H, ddq, J = 15.2, 8.4, 1.6 Hz, $C\mathbf{H}CH_3$), 5.31 (1H, m, $CH_3CH\mathbf{CH}$), 7.20-7.30 (5H, m, Ar**H**). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 51.3, 65.3, 78.1, 126.6, 127.7, 127.9, 128.3, 129.2, 142.9. IR (neat): 3329 (s), 3029 (m), 2916 (s), 2882 (s), 1493 (s), 1014 (s), 698 (s) cm^{-1}. HRMS-(ESI+): for $C_{12}H_{16}O_2Na$ calc'd: 215.1046 $(M+Na)^+$, observed: 215.1048 $(M+Na)^+$. The unpurified reaction mixture was purified on silica gel with 50% ethyl acetate/hexanes as the eluant to afford a white solid in 82% yield (52 mg). R_f = 0.44 (50% ethyl acetate, stain in PMA).

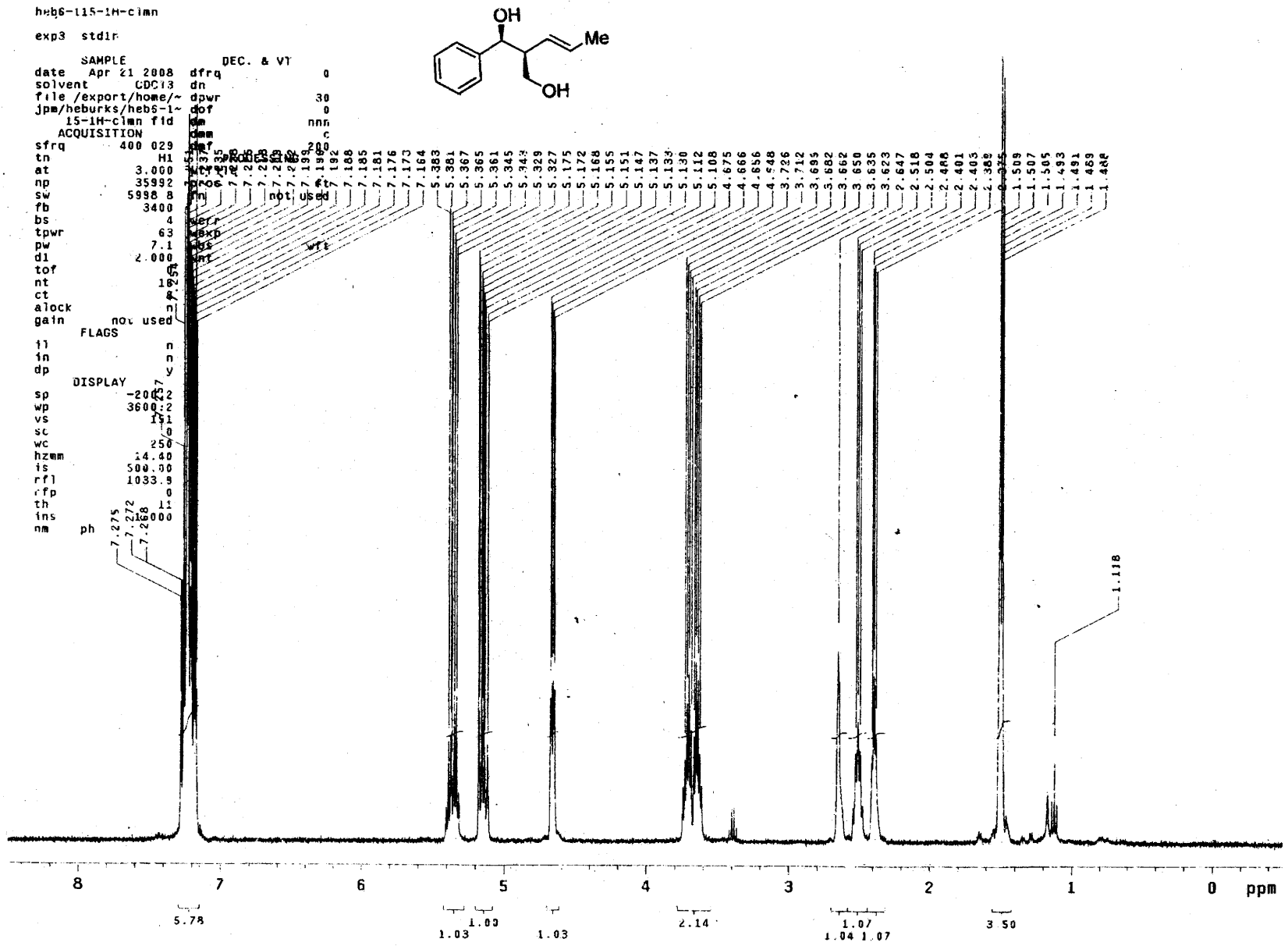
Proof of Enantiopurity. Enantiopurity was determined by treatment of 1-phenyl-2-propenyl-propane-1,3-diol with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid at 60 °C for 5 min. The unpurified mixture was passed through a silica gel plug with 10% ethyl acetate/hexanes as the eluant The resultant ketal was compared to racemic 1-phenyl-2-propenyl-propane-1,3-diol, which was formed from the diboration of *trans*-piperylene with tricyclohexylphosphine (see 3.5.5. General Procedure for Diene Diboration/Allylation/Oxidation).

Chiral GLC (β-dex, Supelco, 140 °C) – analysis of (1S,2S)-1-phenyl-2-((E)-prop-1-enyl)propane-1,3-diol – from acetonide protection.



racemic

diboration/allylation/oxidation reaction product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pw 7.1
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tof
nt
ct
alock
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in n
dp y
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is 500.00
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rfp 0
th 11
ins 1.000
nm ph
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dn
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
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wft
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OH
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5.381
5.367
5.365
5.361
5.345
5.329
5.327
5.175
5.172
5.168
5.155
5.151
5.147
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4.656
4.648
3.726
3.712
3.695
3.682
3.662
3.650
3.635
3.623
2.647
2.518
2.504
2.488
2.401
2.403
2.388
1.509
1.507
1.505
1.493
1.491
1.469
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1.118
8
7
6
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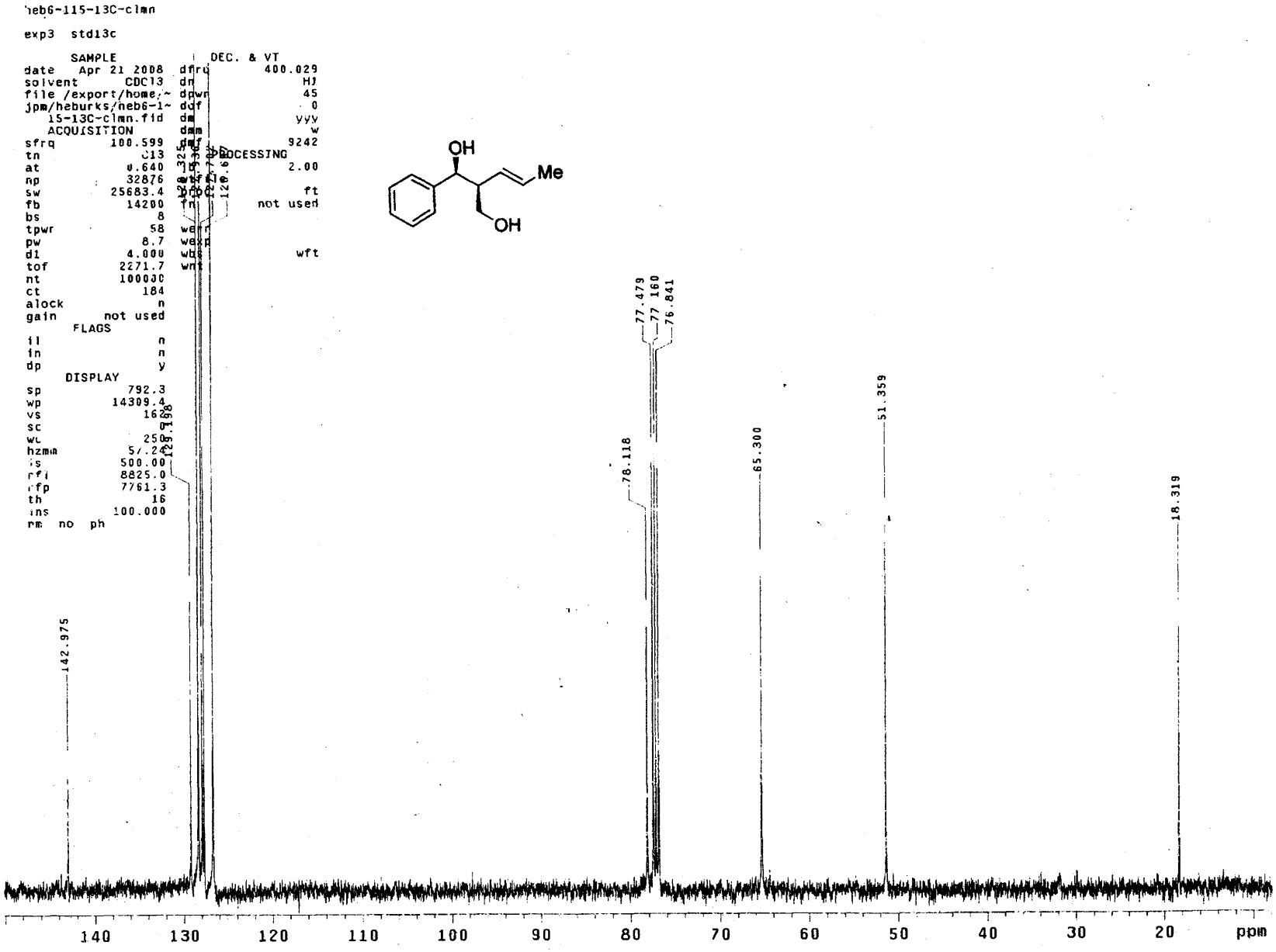
1.07
3.50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is 500.00
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ddf 0
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dmm w
dmf 9242
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ft
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wft
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Me
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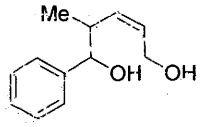
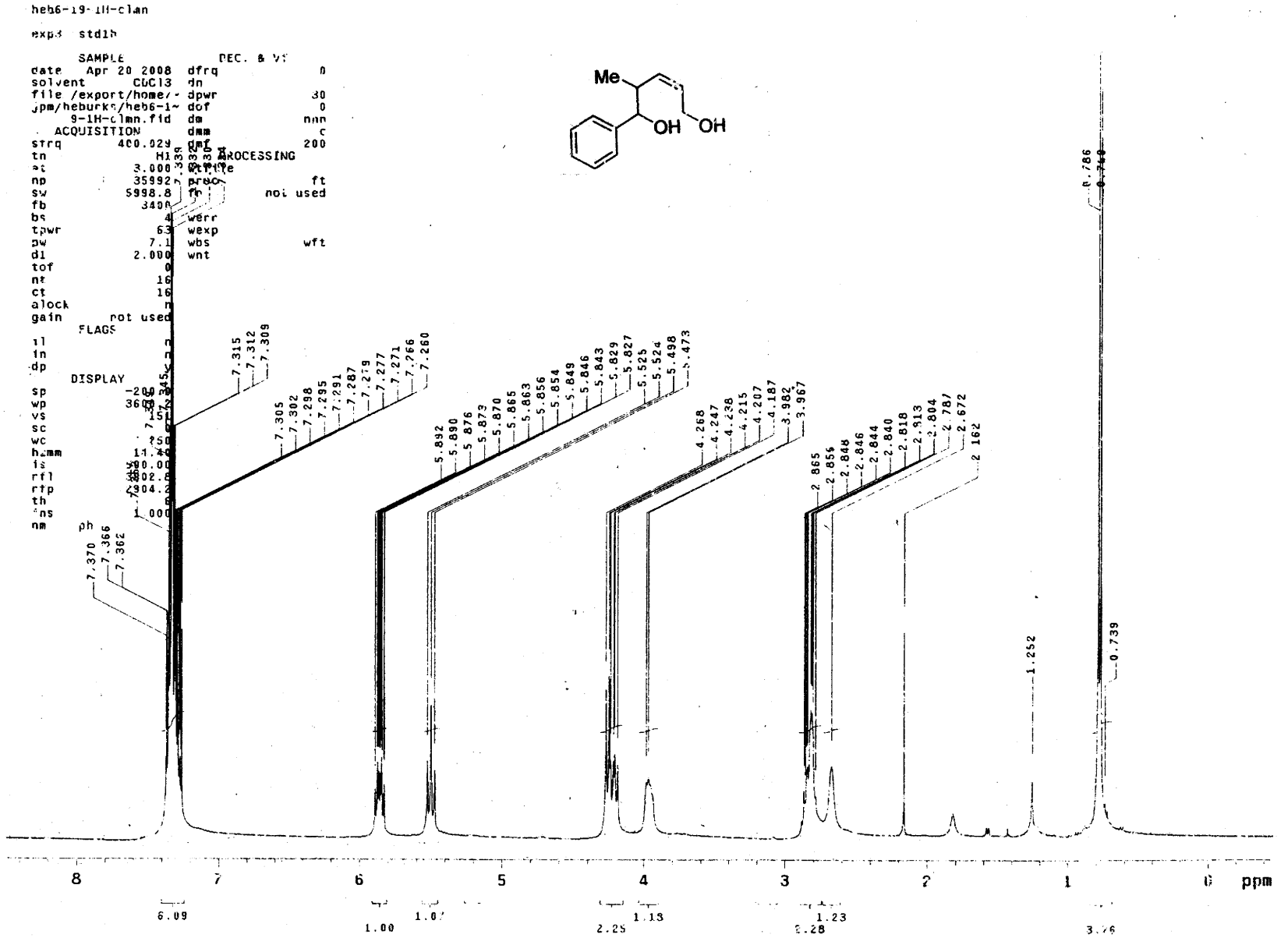
18.319
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

3.5.6. Ligand-Free Diboration/Allylation/Oxidation of trans-Piperylene.

In a dry box, a 6-dram vial with magnetic stir bar was charged with $Pt_2(dba)_3$ (24 mg, 22.0 μmol) and toluene (4.4 mL, 0.1 M). After stirring for 1 h, $B_2(pin)_2$ (117 mg, 0.462 mmol) was added to the mixture followed by *trans*-piperylene (30.0 mg, 0.440 mmol). The vial was sealed with a polypropylene cap, removed from dry box, and stirred at 80 °C for 14 h. The reaction mixture was cooled to ambient temperature and charged with freshly washed (10% sodium carbonate followed by sodium sulfite) and distilled benzaldehyde (50 μL, 0.46 mmol). The reaction was allowed to stir at room temperature for 24 h at which time the reaction mixture was cooled to 0 °C (ice/water) and charged with tetrahydrofuran (3 mL), 3 M sodium hydroxide (2 mL), and 30% hydrogen peroxide (1 mL). The reaction was gradually warmed to room temperature and allowed to stir for 12 h at which time the vial was cooled to 0 °C (ice/water). Saturated sodium thiosulfate was added dropwise over 5 min, the reaction mixture was diluted with ethyl acetate and transferred to a separatory funnel. The aqueous and organic layers were separated, the aqueous layer was rinsed three times with ethyl acetate. The organic extracts were combined and washed with brine. The organic layer was dried (Na_2SO_4), filtered, and volatiles were removed by rotary evaporation. The unpurified reaction mixture was purified on silica gel with 50% ethyl acetate/hexanes as the eluant to afford a clear oil in 58% yield (49 mg).



(*Z*)-4-Methyl-5-phenylpent-2-ene-1,5-diol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (3H, d, J = 6.8 Hz, C**H**$_3$CH), 2.67 (1H, br s, O**H**), 2.84 (1H, br s, O**H**), 2.80-2.86 (1H, m, C**H**CH$_3$), 3.92-3.98 (1H, m br, C**H**$_A$H$_B$OH), 4.21 (1H, dd, J = 12.2, 8 2 Hz, CH$_A$**H**$_B$OH), 4.26 (1H, d, J = 8.4 Hz, PhC**H**), 5.49 (1H, t, J = 10.4 Hz, H$_3$CCHC**H**C), 5.82-5.89 (1H, m, CC**H**CH$_2$OH), 7.27-7.30 (5H, m, Ar**H**). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 40.1, 58.1, 78.2, 126.9, 128.0, 128.4, 130.2, 136.2, 142.7. IR (neat): 3331 (br s), 3028 (m), 2963 (m), 2928 (m), 2874 (m), 1454 (s), 1030 (s), 1002 (s), 762 (s), 700 (s) cm^{-1}. HRMS-(ESI+): for $C_{12}H_{16}O_2Na$ calc'd: 215.1048 $(M+Na)^+$, observed: 215.1043 $(M+Na)^+$. The unpurified reaction mixture was purified on silica gel with 50% ethyl acetate/hexanes as the eluant to afford a clear oil in 58% yield (49 mg). R_f = 0.33 (50% ethyl acetate, stain in PMA).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gain not used
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5.890
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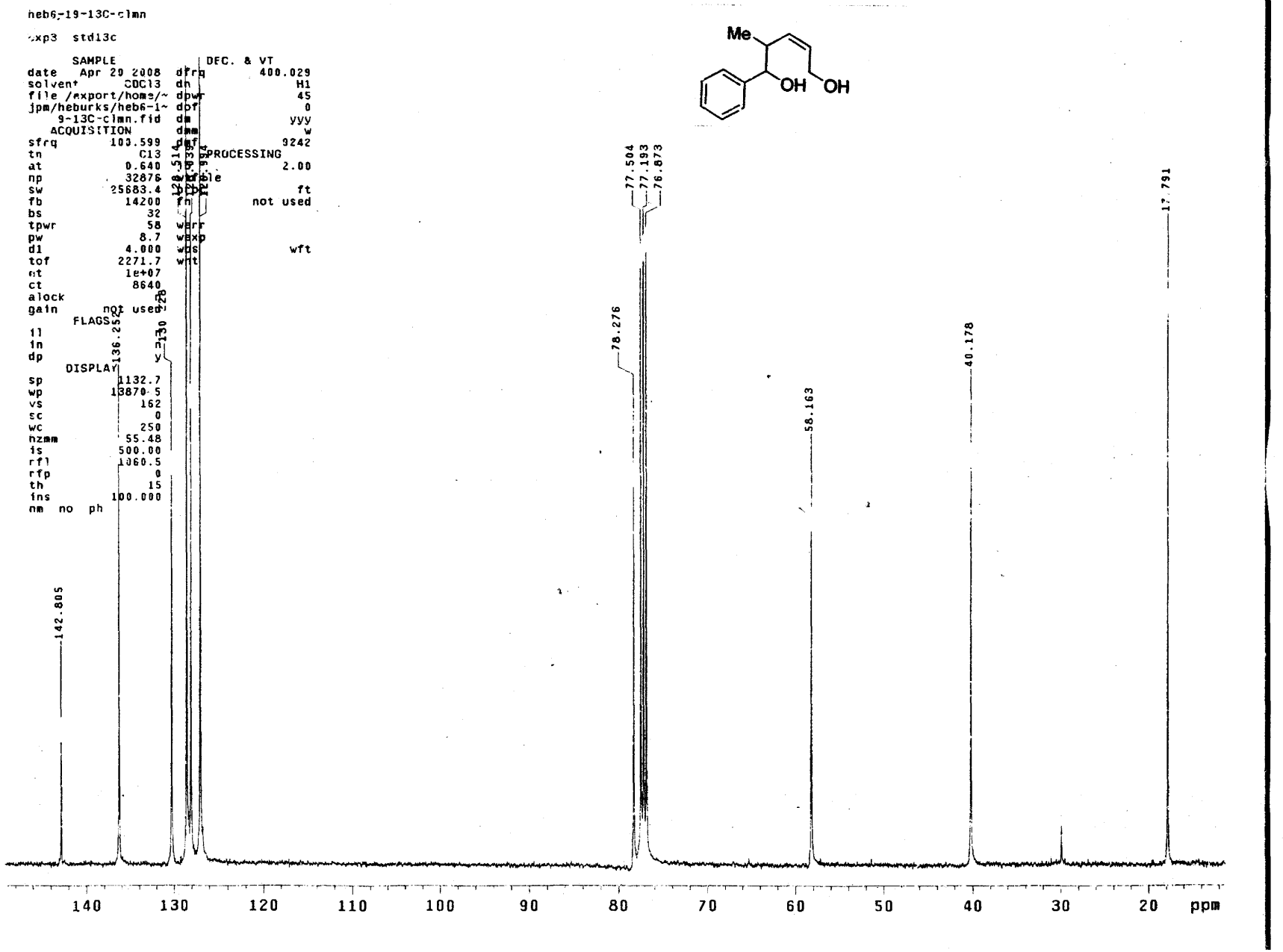
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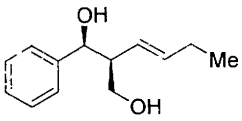
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

3.5.7. General Procedure for Diene Synthesis.

In the dry box, to a flame-dried 250-mL round-bottomed flask equipped with a magnetic stir bar was added potassium *tert*-butoxide (732 mg, 6.53 mmol) and triphenylphosphonium bromide (2.80 g, 7.83 mmol). The flask was sealed with a septum, removed from the dry box, and placed under a nitrogen atmosphere. The flask was charged with THF (8.7 mL, 0.25 M) and the yellow suspension was allowed to stir for 5 min at room temperature. *trans*-Cinnamaldehyde was added dropwise over 5 min to the yellow suspension and the reaction mixture was allowed to stir for 20 min. Solids were removed by filtration over Celite and the unpurified yellow oil was purified by column chromatography with pentanes as the eluant to afford *trans*-1-phenyl-1,3-butadiene as a clear oil (283 mg, 77% yield). Spectral data for dienes are in accordance with the literature: *trans*-1-Phenyl-1,3-butadiene,[32] *trans*-1-cyclohexyl-1,3-butadiene,[33] *trans*-1,3-decadiene,[34] *trans*-6-phenyl-1,3-hexadiene,[32] *trans*-5,5-dimethyl-1,3-hexadiene.[35]

3.5.8. Substrate Scope for Diene Diboration/Allylation/Oxidation.

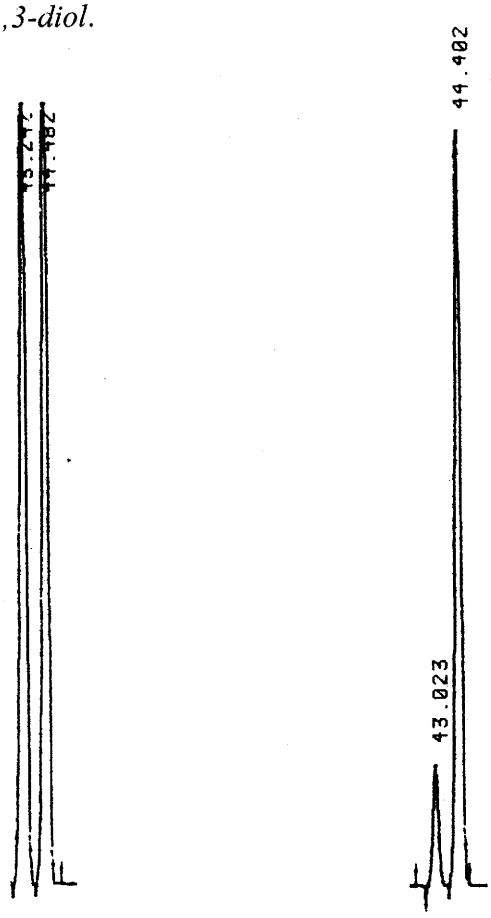


(1*S*,2*S*)-2-((*E*)-But-1-enyl)-1-phenylpropane-1,3-diol (Table 3.11, entry 1). ^{1}H (500 MHz, $CDCl_3$) δ 0.83 (3H, t, J = 7.5 Hz, $\mathbf{H_3}CH_2$), 1.91 (2H, p, J = 7.5 Hz, $CH_3\mathbf{H_2}$), 2.57 (1H, m, $\mathbf{H}CH_2OH$), 3.72 (1H, dd, J =10.5, 4.5 Hz, $HO\mathbf{H_A}H_BCH$), 3.80 (1H, dd, J = 10.5, 7.3 Hz, $HOH_A\mathbf{H_B}CH$), 4.73 (1H, d, J = 7.5 Hz, $PhC\mathbf{H}OH$), 5.16 (1H, ddd, J = 15.5, 8.7, 1.2 Hz, $C\mathbf{H}CHEt$), 5.42 (1H, dt, J = 15.5,

(32) Yeh, K. -L.; Liu, B.; Lo, C. –Y.; Huang, H. –L.; Liu, R. –S. *J. Am. Chem. Soc* **2002**, *124*, 6510.
(33) Habrant, D.; Stengel, B ; Meunier, S.; Mioskowski, C. *Chem. –Eur. J.* **2007**, *13*, 5433.
(34) Meyers, A. I.; Ford, M. E. *J. Org. Chem.* **1976**, *41*, 1735.
(35) Roversi, E.; Monnat, F.; Vogel, P.; Schenk, K.; Roversi, P. *Helv. Chim. Acta* **2002**, *85*, 733.

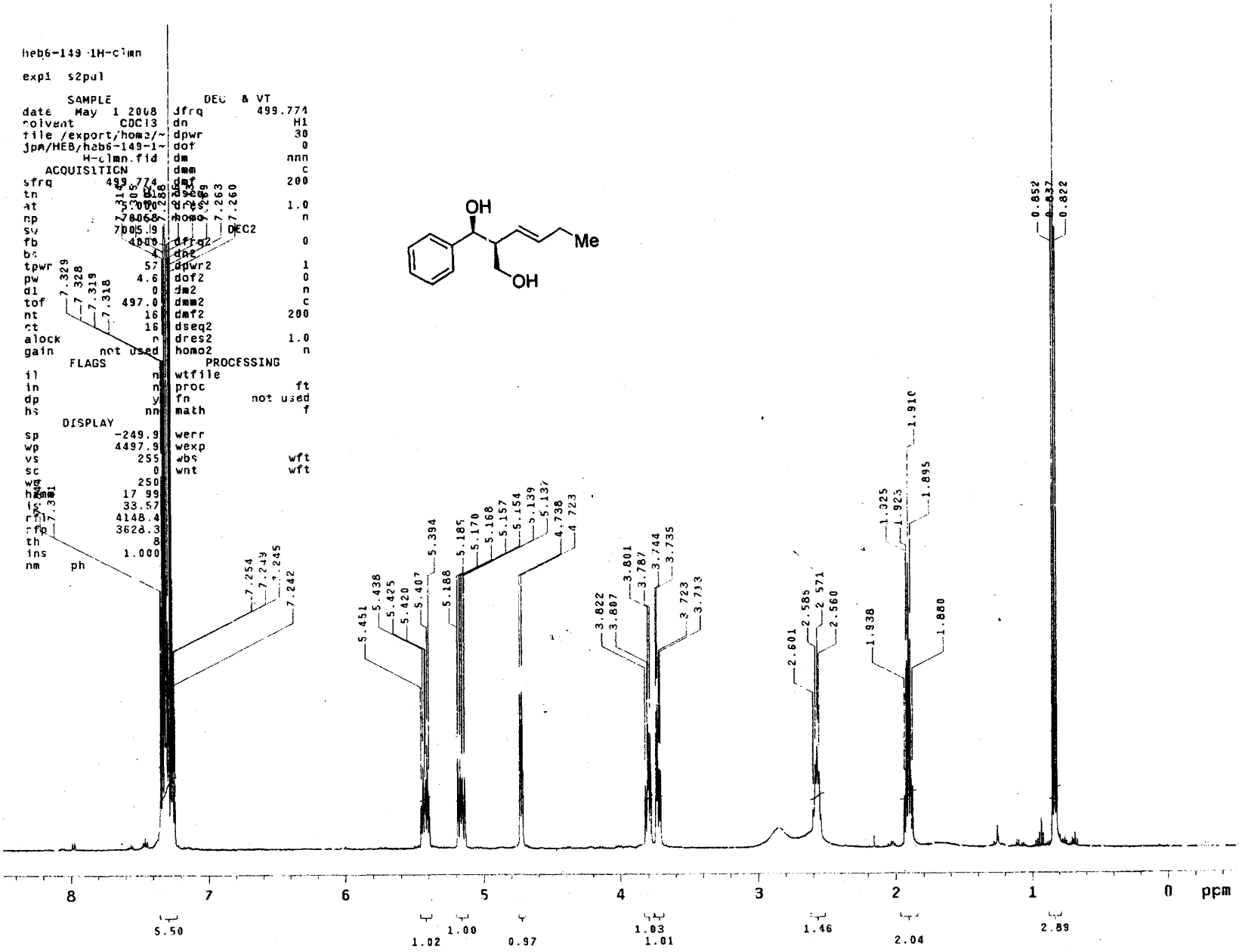
6.5 Hz, CHCHEt), 7.24-7.34 (5H, m, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 25.8, 51.4, 65.4, 78.2, 125.5, 126.7, 127.7, 128.3, 136.4, 143.0. IR (neat): 3370 (br s), 3062 (w), 3030 (w), 2961 (s), 2930 (m), 2873 (m), 1492 (w), 1453 (s), 1043 (s), 968 (m), 759 (s), 699 (s) cm^{-1}. HRMS-(ESI+): for $C_{13}H_{18}O_2Na$ calc'd: 229.1204 $(M+Na)^+$, observed: 229.1201 $(M+Na)^+$. The unpurified reaction mixture was purified on silica gel with 50% ethyl acetate/hexanes as the eluant to afford a clear oil in 54% yield (47 mg). R_f = 0.53 (50% ethyl acetate, stain in PMA).

Chiral GLC (β-dex. Supelco, 140 °C) – analysis of the acetonide of (1S,2S)-2-((E)-but-1-enyl)-1-phenylpropane-1,3-diol.



racemic

diboration/allylation/oxidation reaction product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Me
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7.319
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7.260
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5.407
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5.188
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3.822
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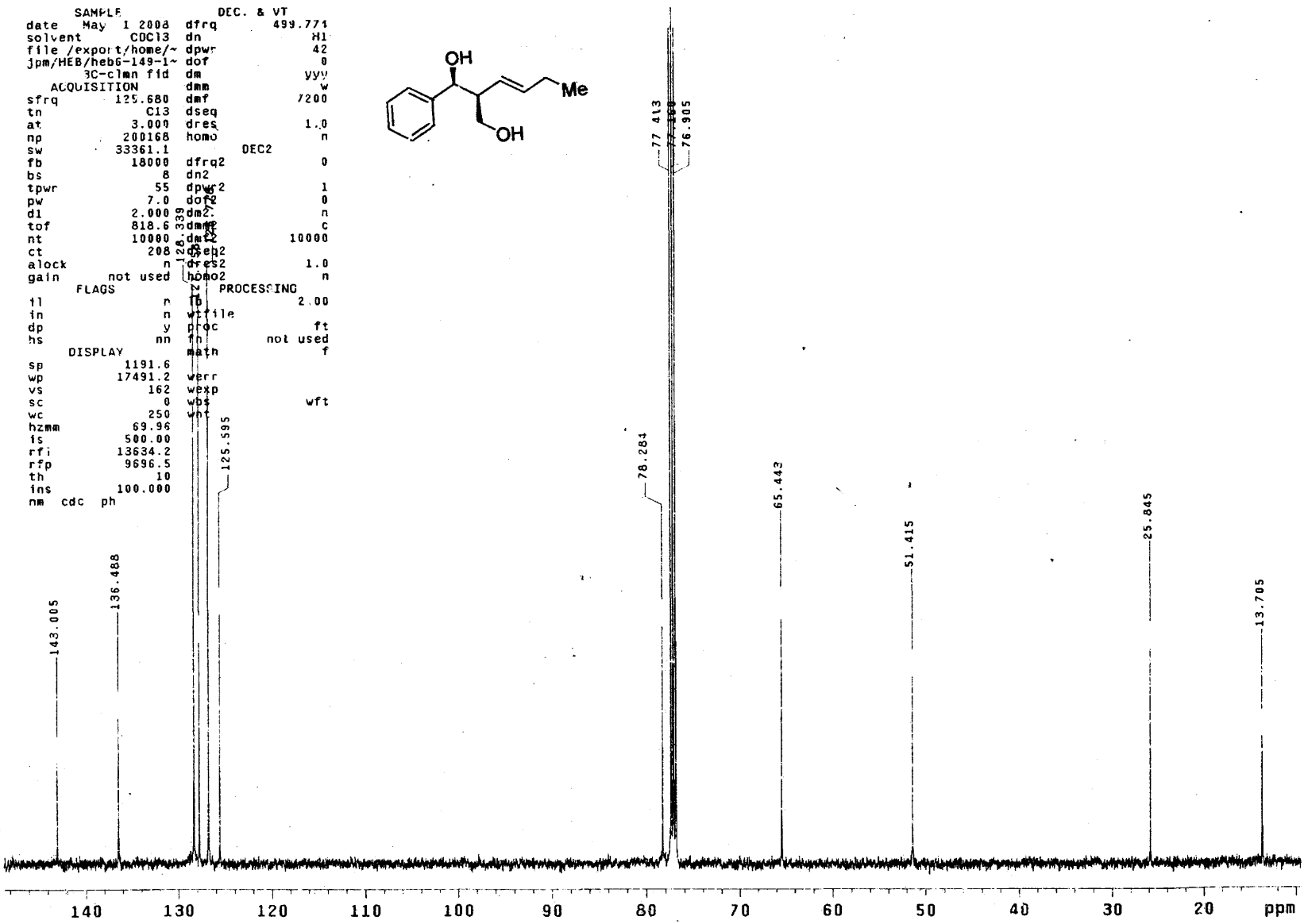
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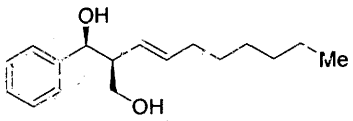
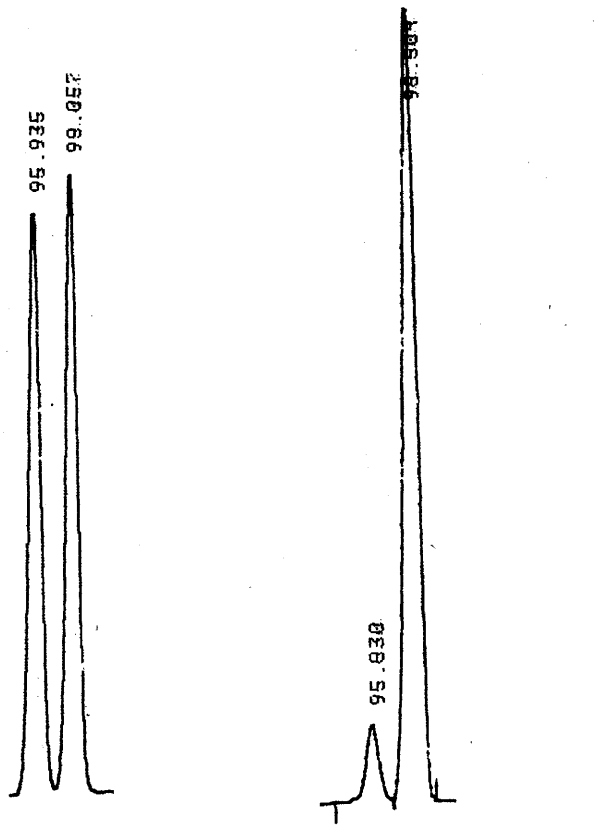
ppm



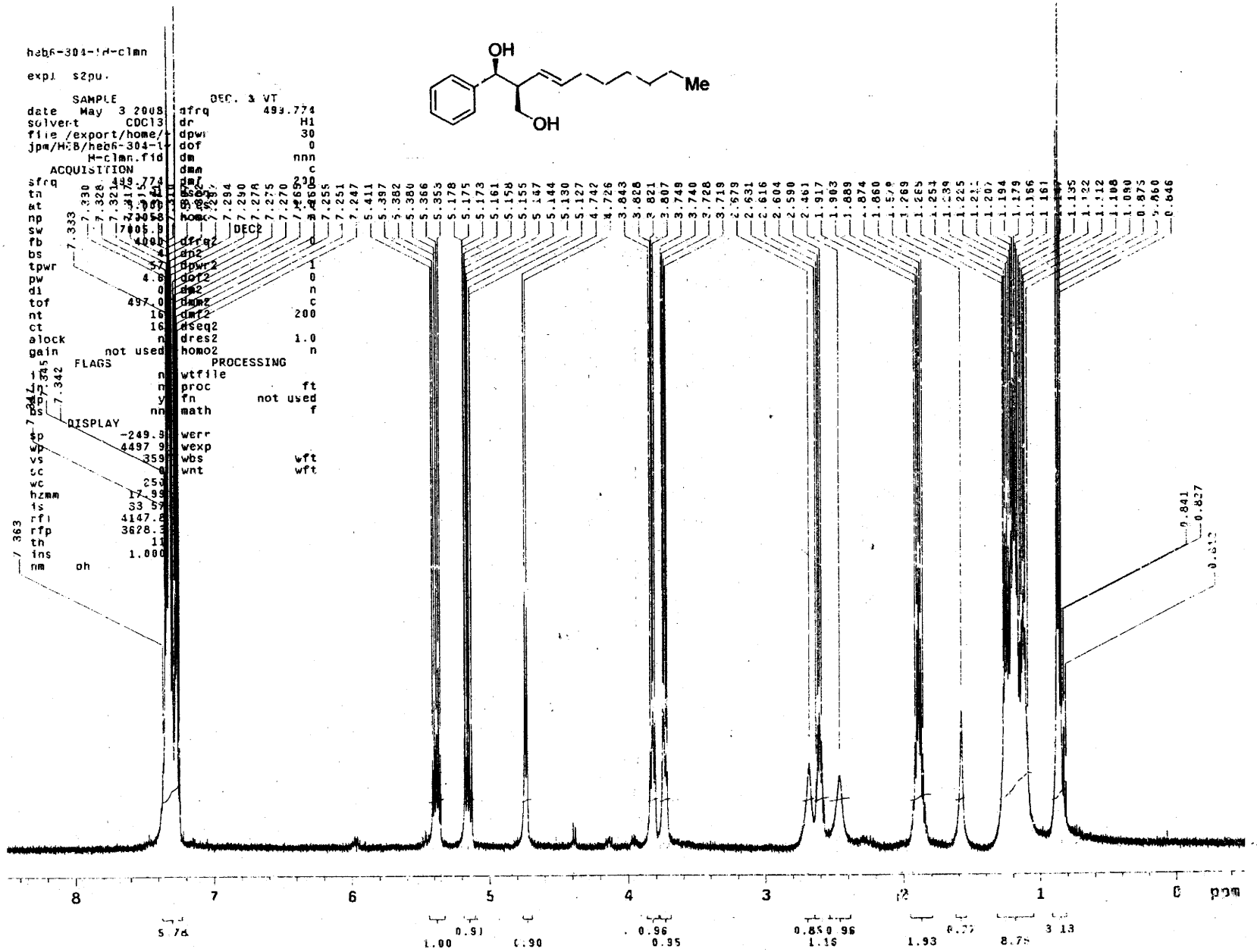
(1*S*,2*S*)-2-((*E*)-Oct-1-enyl)-1-phenylpropane-1,3-diol (Table 3.11, entry 2). ^{1}H (500 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 7.5 Hz, C**H**$_3$CH$_2$), 1.09-1.26 (8H, m, (C**H**$_2$)$_4$), 1.86-1.91 (2H, m, CCC**H**$_2$), 2.46 (1H, br s, OH), 2.59-2.63 (1H, m, C**H**CH$_2$OH), 3.73 (1H, dd, J = 10.5, 4.5 Hz, HOC**H**$_A$H$_B$), 3.82 (1H, dd, J = 11.0, 7.3 Hz, HOCH$_A$**H**$_B$), 4.73 (1H, d, J = 8 Hz, PhC**H**OH), 5.15 (1H, ddt, J = 15.5, 8.5, 1.5 Hz, C**H**CHAlkyl), 5.38 (1H, dt, J = 15.5, 7.0 Hz, CHC**H**Alkyl), 7.24-7.36 (5H, m, Ar**H**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 22.7, 28.7, 29.2, 31.8, 32.7, 51.6, 65.5, 78.2, 126.5, 126.8, 127.8, 128.4, 135.1, 142.9. IR (neat): 3334 (br s), 2954 (s), 2923 (s), 2853 (s), 1453 (s), 1377 (w), 1015 (s), 967 (s), 758 (s), 698 (s) cm^{-1}. HRMS-(ESI+): for $C_{17}H_{26}O_2Na$ calc'd: 285.1831 $(M+Na)^+$, observed: 285.1841 $(M+Na)^+$. The unpurified reaction mixture was purified on silica gel with 50% ethyl acetate/hexanes as the eluant to afford a clear oil in 46% yield (39 mg). R_f = 0.62 (50% ethyl acetate, stain in PMA).

Chiral GLC (β-dex, Supelco, 160 °C) – analysis of the acetonide of (1S,2S)-2-((E)-oct-1-enyl)-1-phenylpropane-1,3-diol



racemic

diboration/allylation/oxidation reaction product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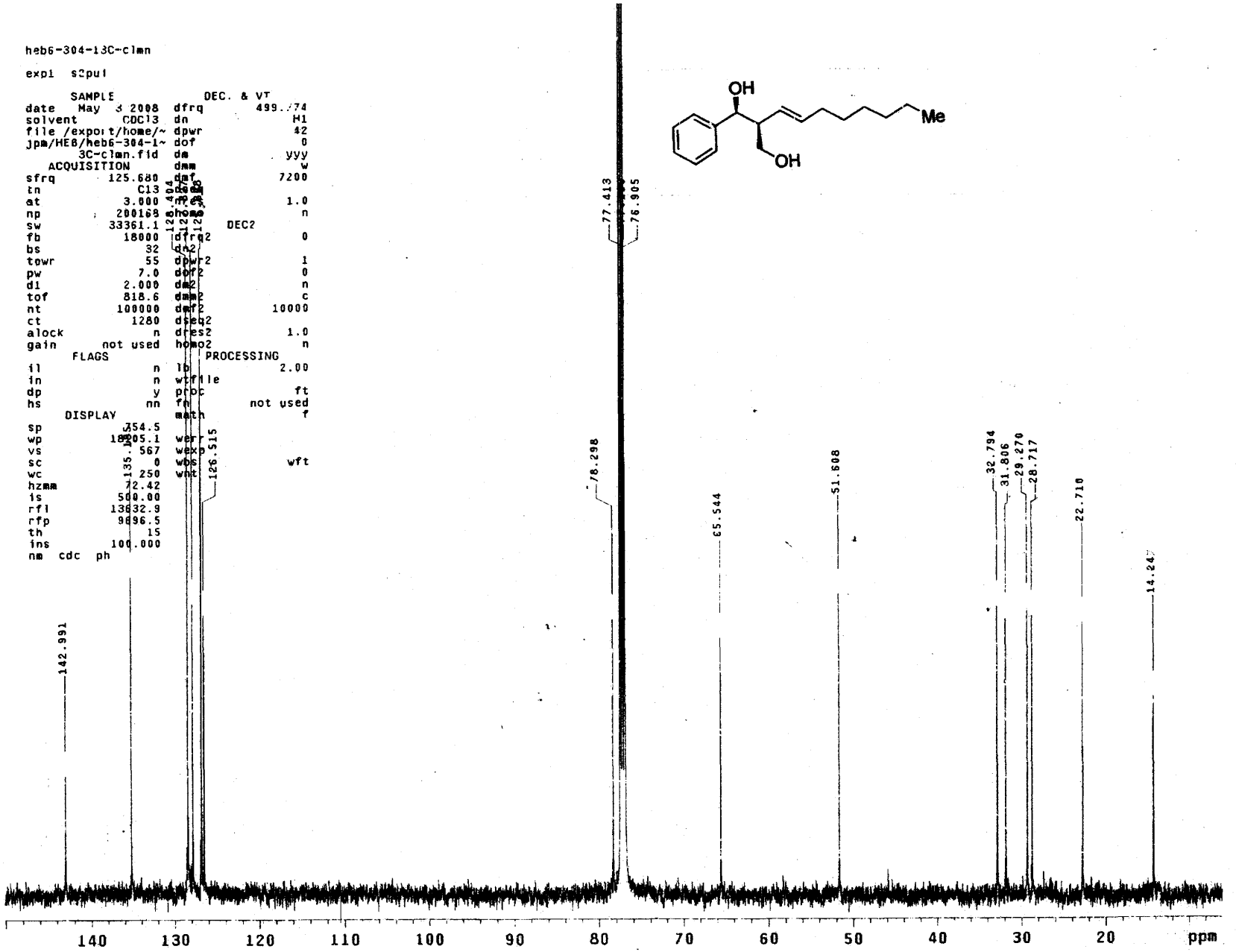
ppm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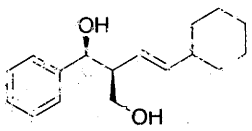
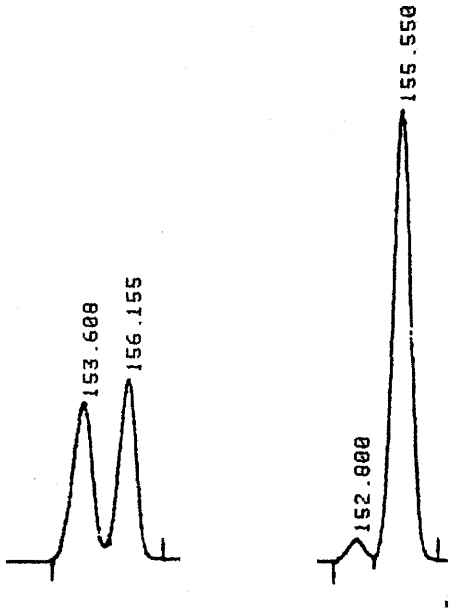


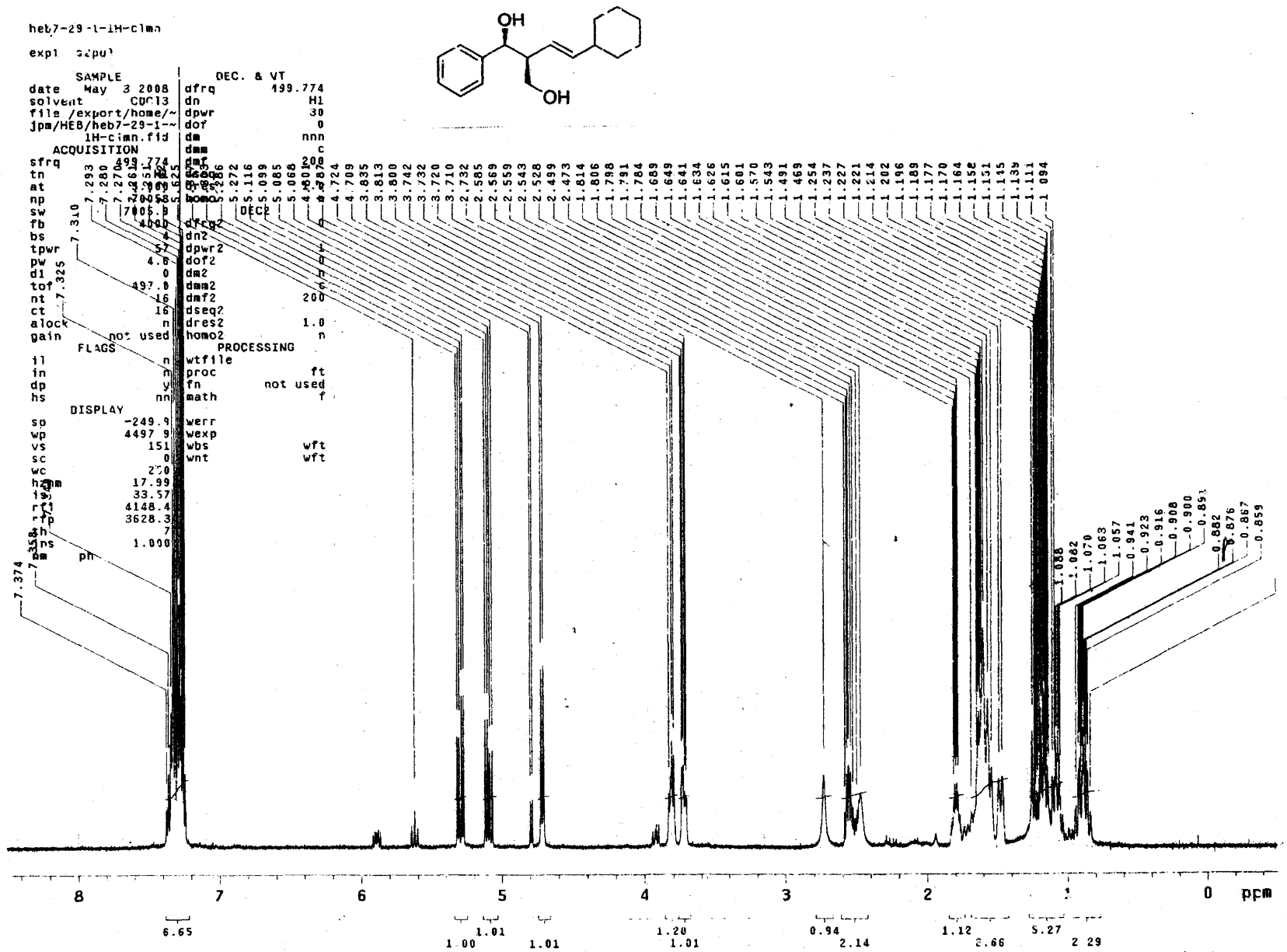
(1*S*,2*S*)-2-((*E*)-2-Cyclohexylvinyl)-1-phenylpropane-1,3-diol (Table 3.11, entry 3). ^{1}H (500 MHz, $CDCl_3$) δ 0.84-0.94 (2H, m, Cy**H**), 1.05-1.23 (4H, m, Cy**H**), 1.46-1.68 (4H, m, Cy**H**), 1.78-1.81 (1H, m, Cy**H**), 2.47 (1H, br s, O**H**), 2.52-2.58 (1H, m, C**H**CH_2OH), 2.73 (1H, br s, O**H**), 3.72 (1H, dd, J = 11.0, 5 Hz, HOC**H**$_A$H$_B$CH), 3.81 (1H, dd, J = 11.0, 6.5, HOCH$_A$**H**$_B$CH), 4.71 (1H, d, J = 7.5 Hz, PhC**H**OH), 5.09 (1H, dd, J = 15.5, 8.5 Hz, C**H**CHCy), 5.29 (1H, dd, J = 15.5, 7.0 Hz, CHC**H**Cy), 7.24-7.37 (5H, m, Ar**H**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.1, 26.3, 32.9, 33.0, 40.9, 51.8, 65.6, 78.4, 124.0, 126.9, 127.8, 128.4, 141.1, 143.1. IR (neat): 3332 (br s), 2920 (s), 2849 (s), 1493 (m), 1448 (s), 1013 (s), 967 (s), 758 (s), 698 (s) cm^{-1}. HRMS-(ESI+): for $C_{17}H_{24}O_2Na$ calc'd: 283.1674 $(M+Na)^+$, observed: 283.1683 $(M+Na)^+$ The unpurified reaction mixture was purified on silica gel with 50% ethyl acetate/hexanes as the eluant to afford a clear oil in 28% yield (21 mg). R_f = 0.59 (50% ethyl acetate, stain in PMA).

Chiral GLC (β-dex, Supelco, 160 °C) – analysis of the acetonide of (1S,2S)-2-((E)-2-cyclohexylvinyl)-1-phenylpropane-1,3-diol



racemic

diboration/allylation/oxidation reaction product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dp y
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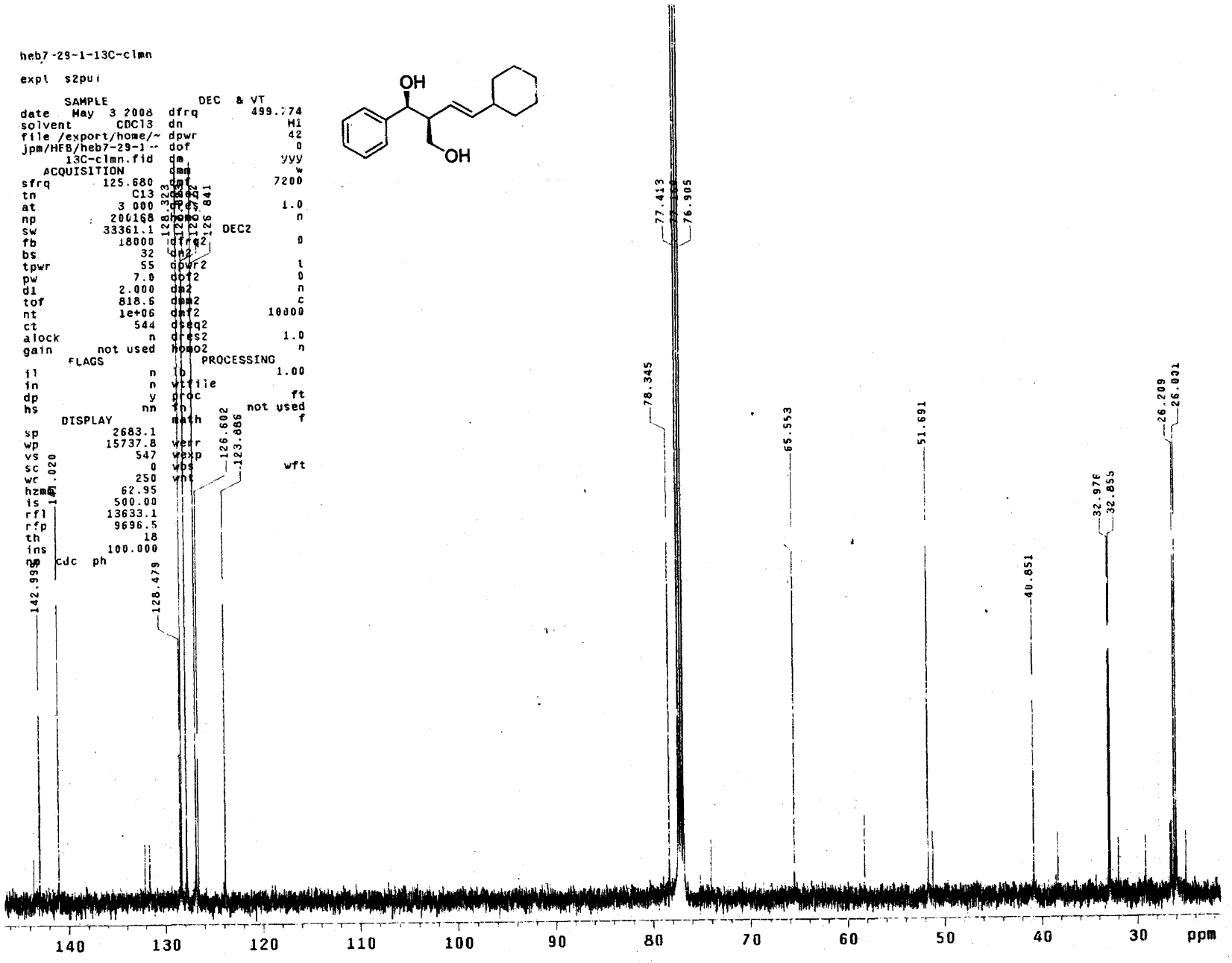
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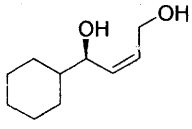
26.209
26.031
140
130
120
110
100
90
80
70
60
50
40
30
ppm

3.5.9. General Procedure for Diene Diboration/Oxidation.

In a dry box, a 6-dram vial with magnetic stir bar was charged with $Pt_2(dba)_3$ (6 mg, 5.5 μmol), (*R,R*)-xylylTADDOLPPh **(*R,R*)-3.33** (9 mg, 13.2 μmol), and toluene (2.20 mL, 0.1 M). After stirring for 1 h, $B_2(pin)_2$ (58.6 mg, 32.1 μmol) was added to the mixture followed by (*E*)-1-cyclohexyl-1,3-butadiene (30.0 mg, 22.0 μmol). The vial was sealed with a polypropylene cap, removed from dry box, and stirred at 60 °C for 14 h. The reaction mixture was cooled to 0 °C (ice/water) and charged with tetrahydrofuran (3 mL), 3 M sodium hydroxide (2 mL), and 30% hydrogen peroxide (1 mL). The reaction was gradually warmed to room temperature and allowed to stir for 12 h at which time the vial was cooled to 0 °C (ice/water). Saturated sodium thiosulfate was added dropwise over 5 min, the reaction mixture was diluted ethyl acetate, transferred to a separatory funnel. The aqueous and organic layers were separated, the aqueous layer was rinsed three times with ethyl acetate. The organic extracts were combined and washed with brine. The organic layer was dried (Na_2SO_4), filtered, and volatiles were removed by rotary evaporation. The unpurified reaction mixture was purified on silica gel with 50% ethyl acetate/hexanes as the eluant to afford a clear oil in 80% yield (31 mg).

3.5.10. Characterization of Substrates in Table 3.12.



(*R,Z*)-1-Cyclohexylbut-2-ene-1,4-diol (Table 3.12, entry 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89-1.01 (2H, m, Cy**H**), 1.10-1.25 (3H, m, Cy**H**), 1.34-1.41 (1H, m, Cy**H**), 1.65-1.90 (5H, m, Cy**H**), 2.38 (2H, br s, O**H** x 2), 4.06-4.15 (1H, m, CH_AH_BOH), 4.06-4.15 (1H, m, C**H**OH), 4.29 (1H, ddd, J = 12.8, 7.6, 1.6 Hz,

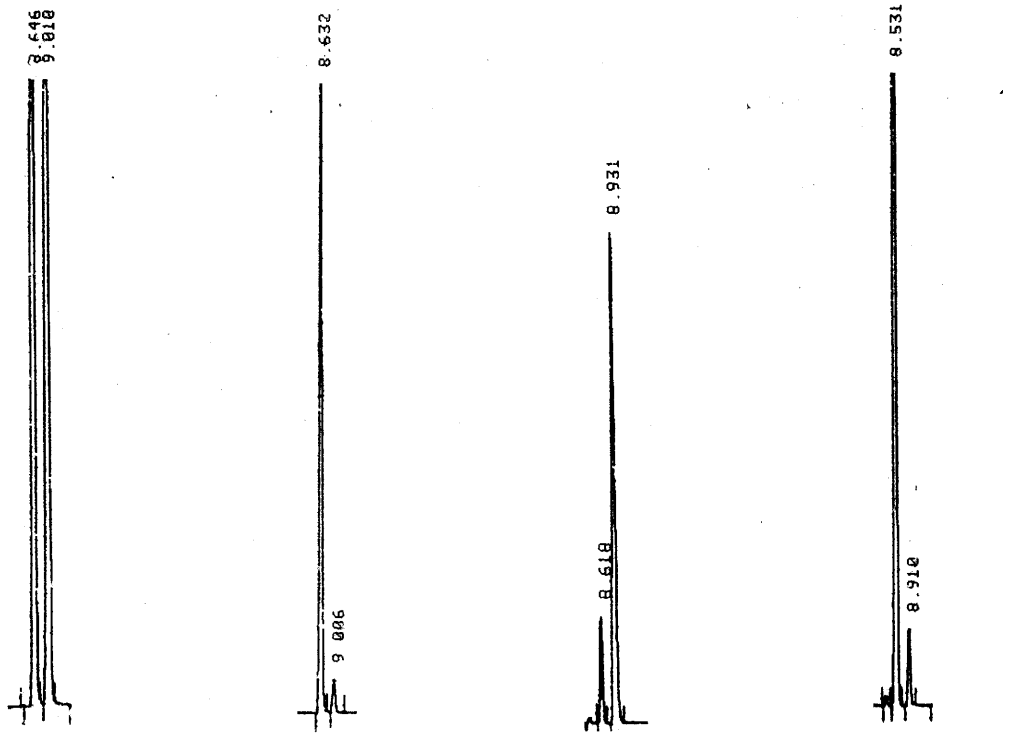
CH_AH_BOH), 5.55 (1H, ddt, J = 11.2, 8.4, 1.6 Hz, CHOHC**H**C), 5.77 (1H, m, CC**H**CH_2OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 26.2, 26.6, 28.7, 28.8, 43.9, 58.8, 72.2, 130.9, 133.9. IR (neat): 3325 (br s), 2923 (s), 2851 (s), 2300 (w), 1449 (m), 1015 (s) cm^{-1}. HRMS-(ESI+): for $C_{10}H_{18}O_2Na$ calc'd: 193.1204 $(M+Na)^+$, observed: 193.1199 $(M+Na)^+$. The unpurified reaction mixture was purified on silica gel with 50% ethyl acetate/hexanes as the eluant to afford a clear oil in 80% yield (31 mg). R_f = 0.17 (50% ethyl acetate, stain in PMA).

Proof of Configuration.

Procedure for ozonlysis of the 1,4-dihydroxylation product. To a 25-mL round-bottomed flask with magnetic stir bar was added (*R,Z*)-1-cyclohexylbut-2-ene-1,4-diol (11 mg, 64.6 μmol) and dichloromethane (1.6 mL). The flask was cooled to -78 °C (dry ice/isopropanol) and treated with ozone until a pale blue color was observed. To the cooled solution was added methanol (1.6 mL) and sodium borohydride (24 mg, 37.8 mmol). The reaction mixture was gradually warmed to room temperature and allowed to stir for 2 h at which time volatiles were removed by rotary evaporation. The solid residue was dissolved in ethyl acetate and water and transferred to a separatory funnel. The aqueous and organic layers were separated, and the aqueous layer was washed three times with ethyl acetate. The organic extracts were combined and washed with brine, dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. The resultant oil was purified by column chromatography on silica gel with 50% ethyl acetate/hexanes as the eluant to afford a clear oil in 79% yield (9.3 mg). The oil was treated with 2,2-dimethoxypropane

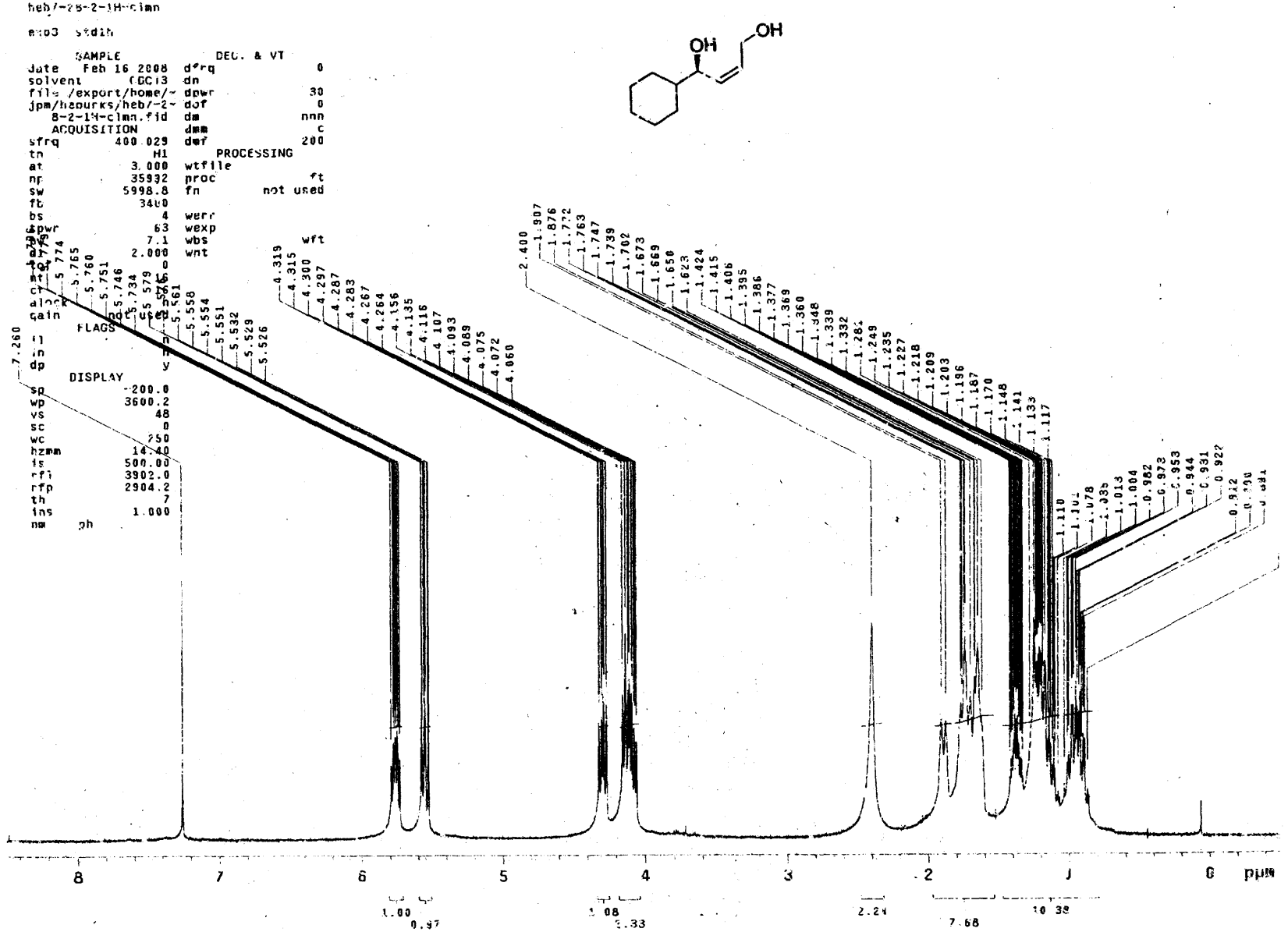
and catalytic *p*-toluenesulfonic acid at 60 °C for 5 min. The unpurified mixture was passed through a silica gel plug with 10% ethyl acetate/hexanes as the eluant. The resultant ketal was compared to racemic ketal of 1-cyclohexylethane-1,2-diol prepared from treatment of vinyl cyclohexane with osmium tetraoxide and 4-methyl morpholine N-oxide. The authentic sample was prepared from the Sharpless asymmetric dihydroxylation of vinyl cyclohexane utilizing AD-mix α.[36]

Chiral GLC (β-dex, Supelco, 130 °C) – analysis of the acetonide of 1-cyclohexylethane-1,2-diol



racemic | reaction product | authentic | reaction product and racemic

(36) Becker, H.; King, S. B.; Taniguchi, M.; Vanhessche, K. P. M.; Sharpless, K. B. *J Org. Chem.* **1995**, *60*, 3940.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Date Feb 16 2008
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bs 4
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vs 48
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wc 250
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rfl 3902.0
rfp 2904.2
th 7
ins 1.000
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dpwr 30
dof 0
dm nnn
dmm c
dmf 200
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proc ft
fn not used
werr
wexp
wbs
wnt
wft
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1.406
1.395
1.386
1.377
1.369
1.360
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1.339
1.332
1.249
1.235
1.227
1.218
1.209
1.203
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1.187
1.170
1.148
1.141
1.133
1.117
1.078
1.013
1.004
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0.953
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0.931
0.922
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2.24
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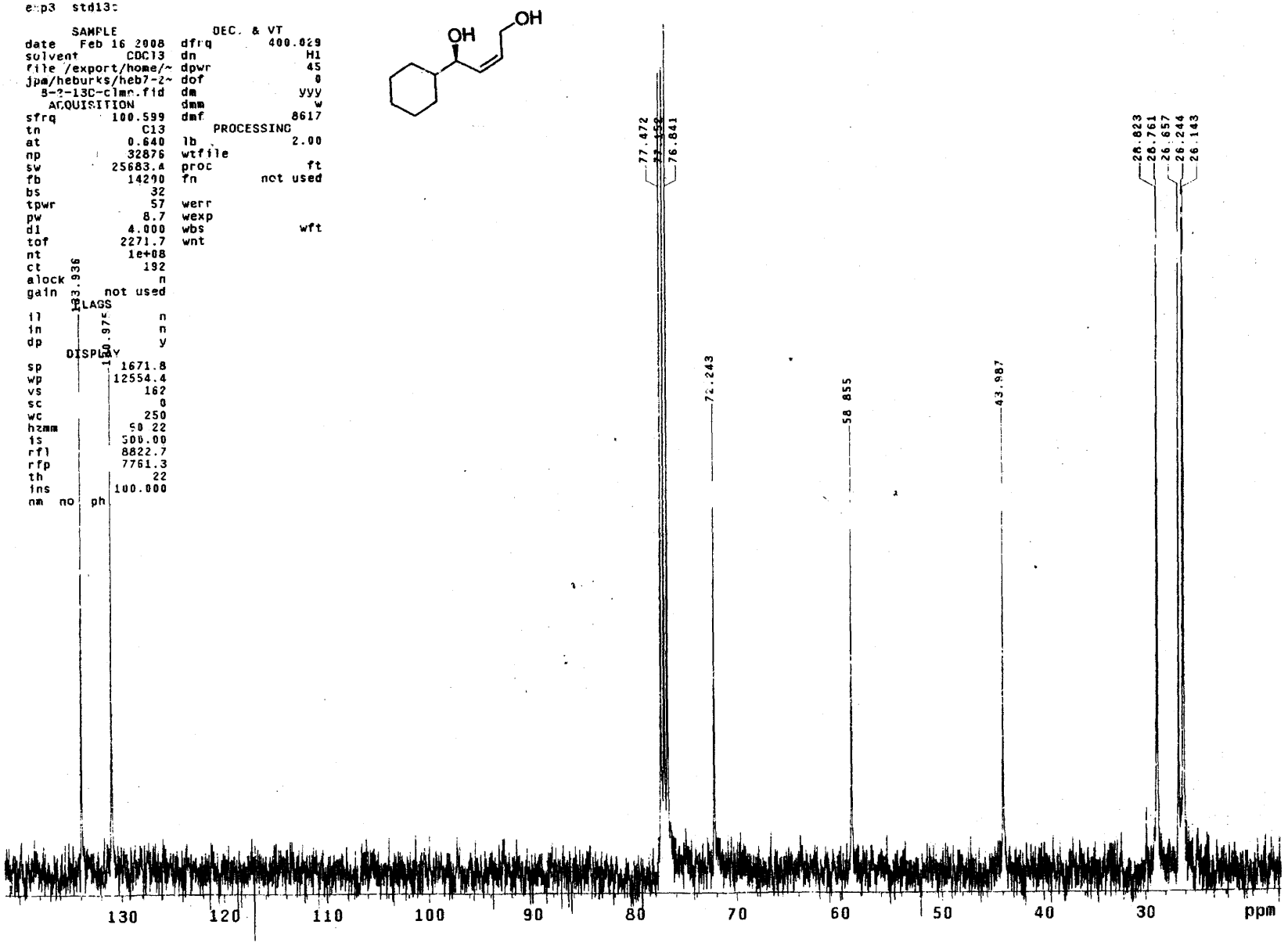
10.38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date Feb 16 2008
solvent CDCl3
file /export/home/~
jpa/heburks/heb7-2~
8-2-13C-clmn.fid
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at 0.640
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fb 14290
bs 32
tpwr 57
pw 8.7
d1 4.000
tof 2271.7
nt 1e+08
ct 192
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp 1671.8
wp 12554.4
vs 162
sc 0
wc 250
hzmm 50.22
is 500.00
rfl 8822.7
rfp 7761.3
th 22
ins 100.000
nm no ph
DEC. & VT
dfrq 400.029
dn H1
dpwr 45
dof 0
dm yyy
dmm w
dmf 8617
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proc ft
fn not used
werr
wexp
wbs wft
wnt
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OH
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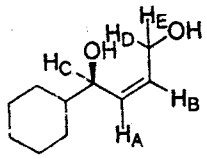
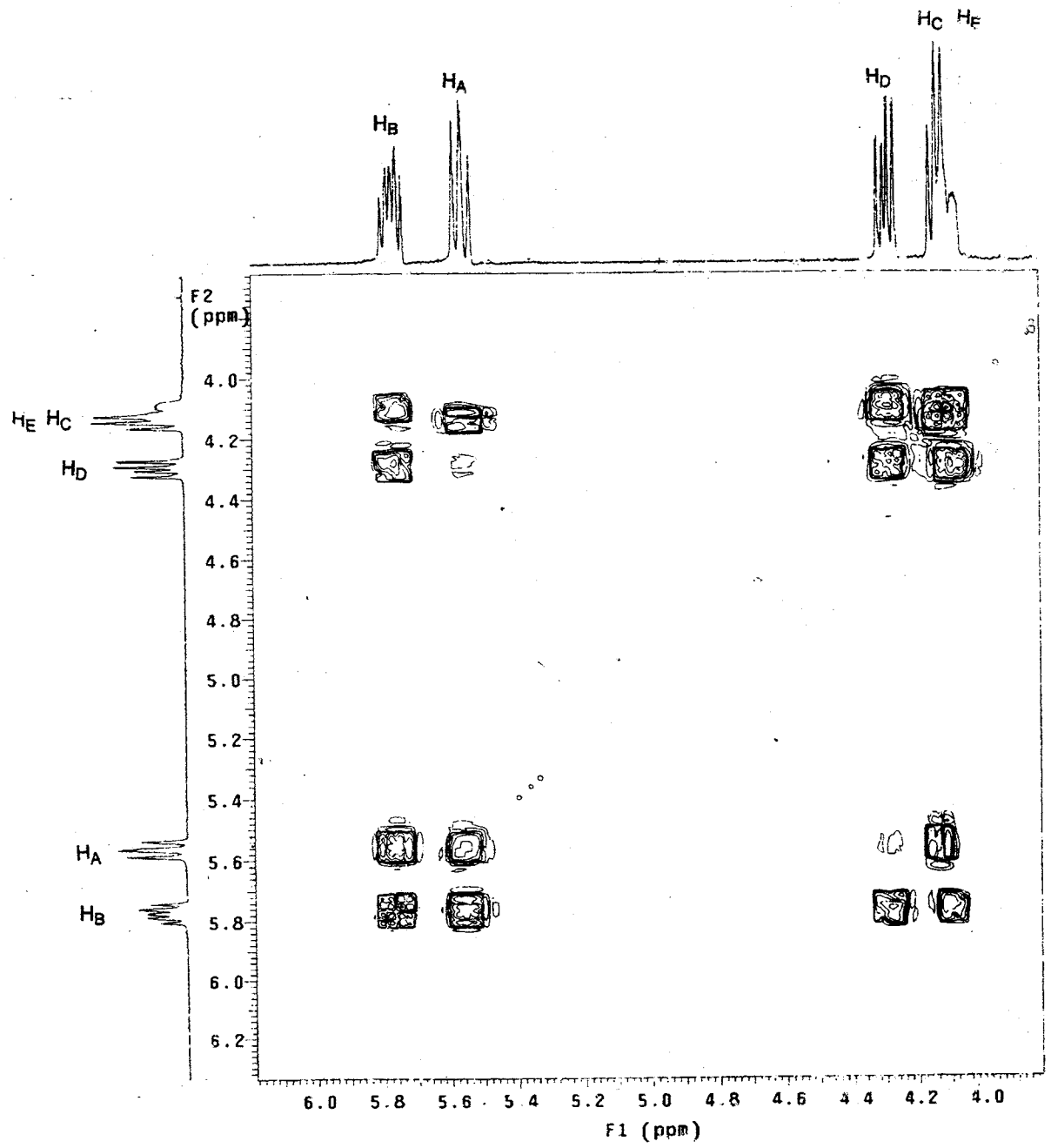
76.841
72.243
58.855
43.987
26.823
26.761
26.657
26.244
26.143
130
120
110
100
90
80
70
60
50
40
30
ppm

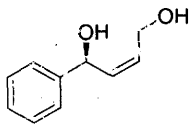
heb7-28-1

Pulse Sequence: COSY
Solvent: CDCl3
Ambient temperature
GEMINI-400B "nmr8"

Relax. delay 1.000 sec
Acq. time 0.180 sec
Width 2845.7 Hz
20 Width 2845.7 Hz
16 repetitions
128 increments
OBSERVE H1, 400.0268157 MHz
DATA PROCESSING
Sq. sine bell 0.090 sec
F1 DATA PROCESSING
Sq. sine bell 0.045 sec
FT size 2048 x 2048
Total time 44 min, 47 sec





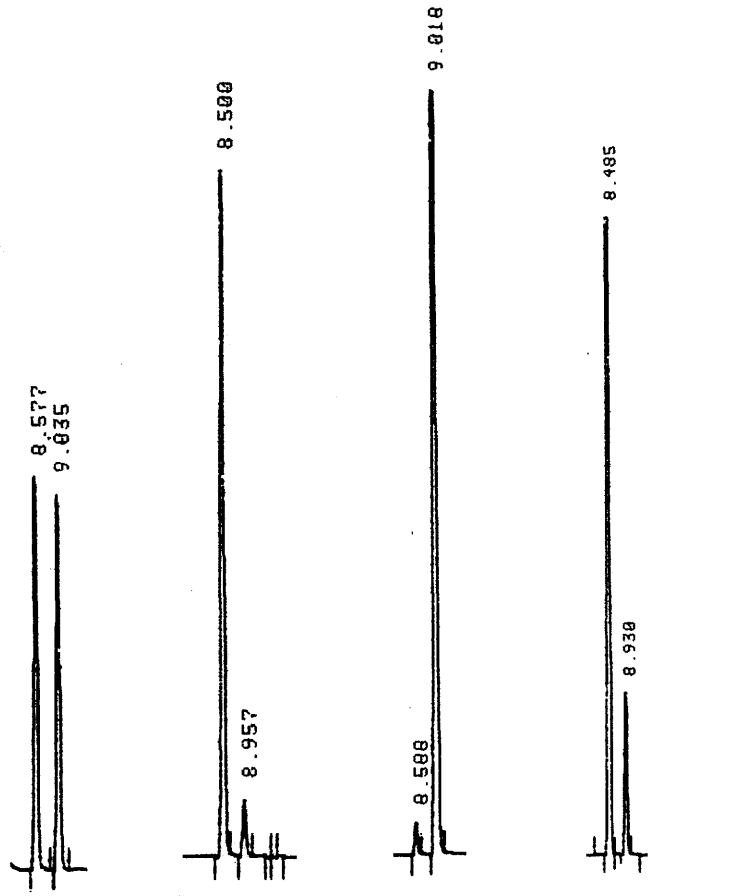


(*S,Z*)-1-Phenylbut-2-ene-1,4-diol (Table 3.12, entry 4). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.8-2.0 (1H, br s, O**H**), 2.3-3.5 (1H, br s, O**H**), 4.23 (1H, dd, J = 13.2, 4.3 Hz, HOC$\mathbf{H_A}$H$_B$), 4.43 (1H, dd, J = 13, 5.5 Hz, HOCH$_A$$\mathbf{H_B}$), 5.57 (1H, d, J = 7.0 Hz, CC**H**CHOH), 5.79-5.81 (1H, m, PhC**H**OH), 5.79-5.81 (1H, m, CC**H**CH$_2$OH), 7.29 (1H, tt, J = 6.8, 2 Hz, *p*-Ar**H**), 7.34-7.40 (4H, m, Ar**H**). ^{13}C NMR (125 MHz, $CDCl_3$) δ 59.0, 70.3, 126.1, 127.9, 128.8, 130.2, 134.6, 143.2. IR (neat): 3319 (br s), 3026 (m), 2923 (m), 2854 (m), 1450 (m), 1016 (s), 968 (s), 845 (s), 696 (s) cm^{-1}. HRMS-(ESI+): for $C_{10}H_{12}O_2Na$ calc'd: 187.0735 $(M+Na)^+$, observed: 187.0741 $(M+Na)^+$. The unpurified reaction mixture was purified on silica gel with 50% ethyl acetate/hexanes as the eluant to afford a white solid in 83% yield (83 mg). R_f = 0.16 (50% ethyl acetate, stain in PMA).

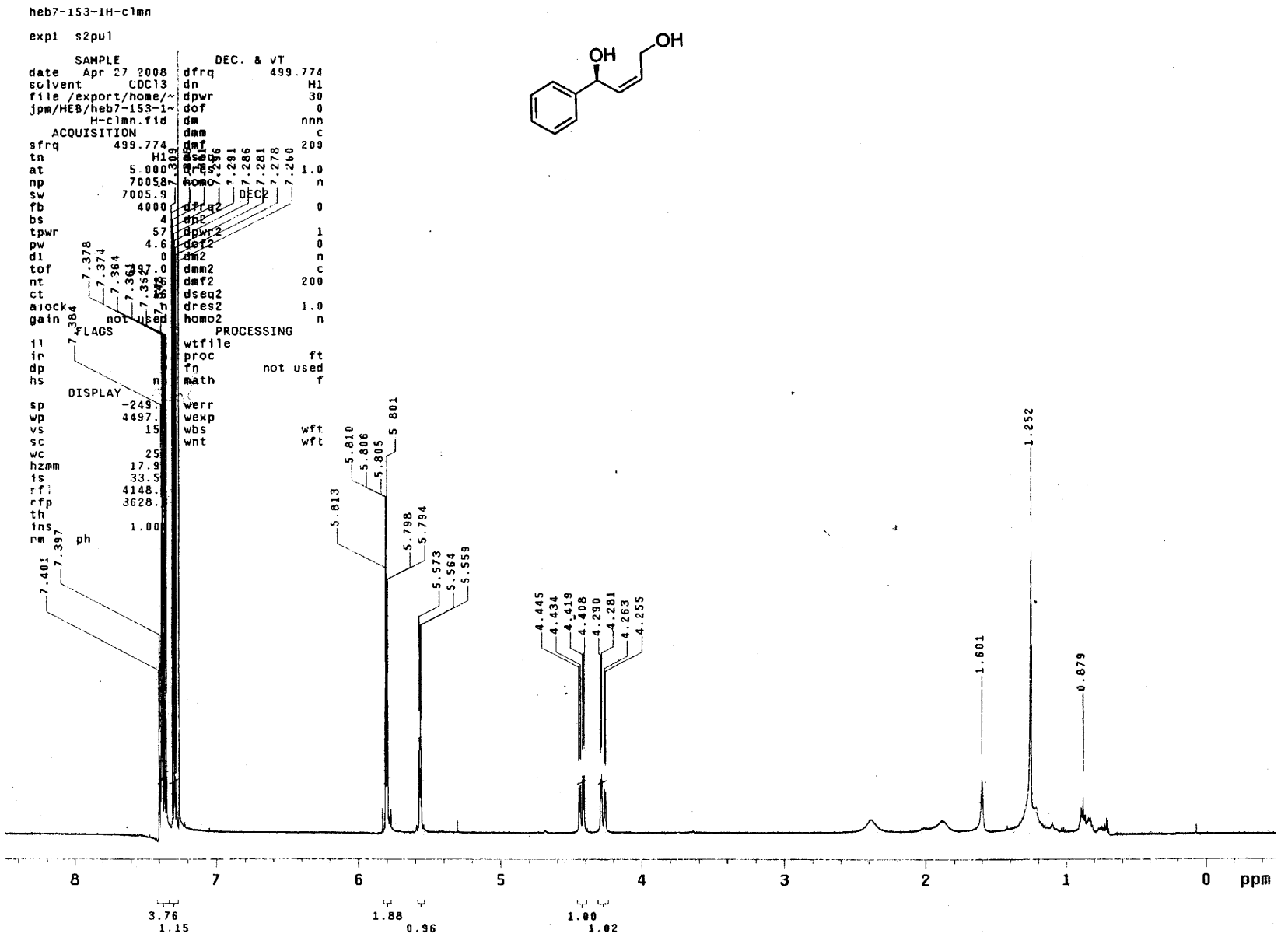
Proof of Configuration.

The 1,4-dihydroxylation product (*S,Z*)-1-phenylbut-2-ene-1,4-diol was treated with ozone in the procedure described for (*R,Z*)-1-cyclohexylbut-2-ene-1,4-diol. The resulting 1,2-diol was treated with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid at 60 °C for 5 min. The unpurified mixture was passed through a silica gel plug with 10% ethyl acetate/hexanes as the eluant. The resultant ketal was compared to racemic ketal of 1-phenyl-ethane-1,2-diol prepared from the dihydroxylation of styrene with osmium tetraoxide and 4-methyl morpholine N-oxide. The authentic sample was prepared from the Sharpless asymmetric dihydroxylation of styrene utilizing AD-mix α.[36]

Chiral GLC (β-dex, Supelco, 140 °C) - analysis of the acetonide of 1-phenylethane-1,2-diol.



racemic | reaction product | authentic | reaction product and racemic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sw 7005.9
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tpwr 57
pw 4.6
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tof 897.0
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ct 8
alock n
gain not used
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sc
wc 25
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is 33.5
rfl 4148.
rfp 3628.
th
ins 1.00
nm ph
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dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
dseq
dres 1.0
homo n
DEC2
dfrq2 0
dn2
dpwr2 1
dof2 0
dm2 n
dmm2 c
dmf2 200
dseq2
dres2 1.0
homo2 n
PROCESSING
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math f
werr
wexp
wbs wft
wnt wft
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OH
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7.378
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7.358
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7.296
7.291
7.286
7.281
7.278
7.260
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5.806
5.805
5.801
5.798
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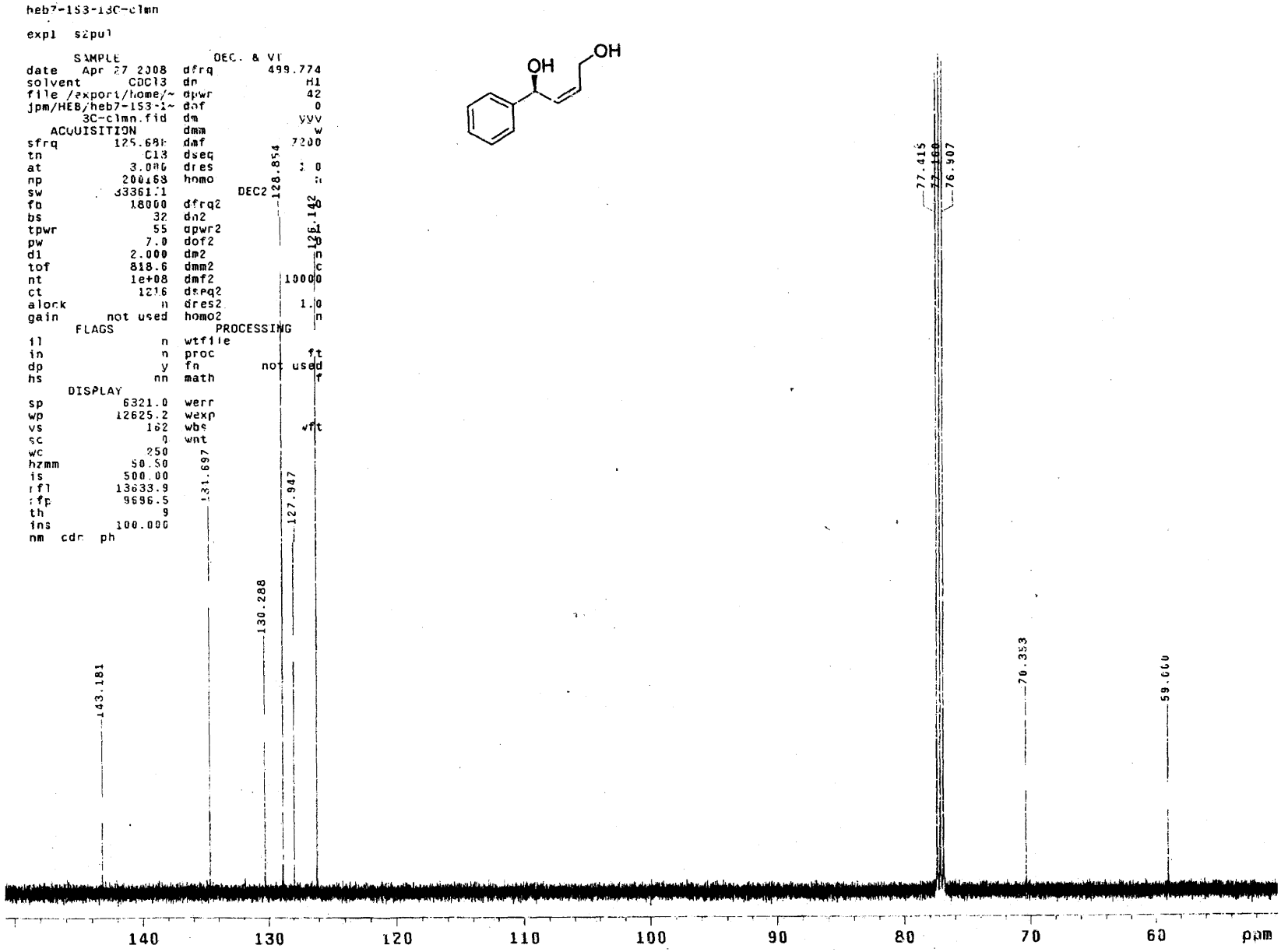
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gain not used
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dp y
hs nn
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is 500.00
rfl 13633.9
rfp 9696.5
th 9
ins 100.000
nm cdc ph
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dmm w
dmf 7200
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dres 1.0
homo n
DEC2
dfrq2
dn2
dpwr2
dof2
dm2 n
dmm2 c
dmf2 19000
dseq2
dres2 1.0
homo2 n
PROCESSING
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math f
werr
wexp
wbs wft
wnt
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127.947
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76.907
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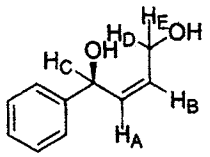
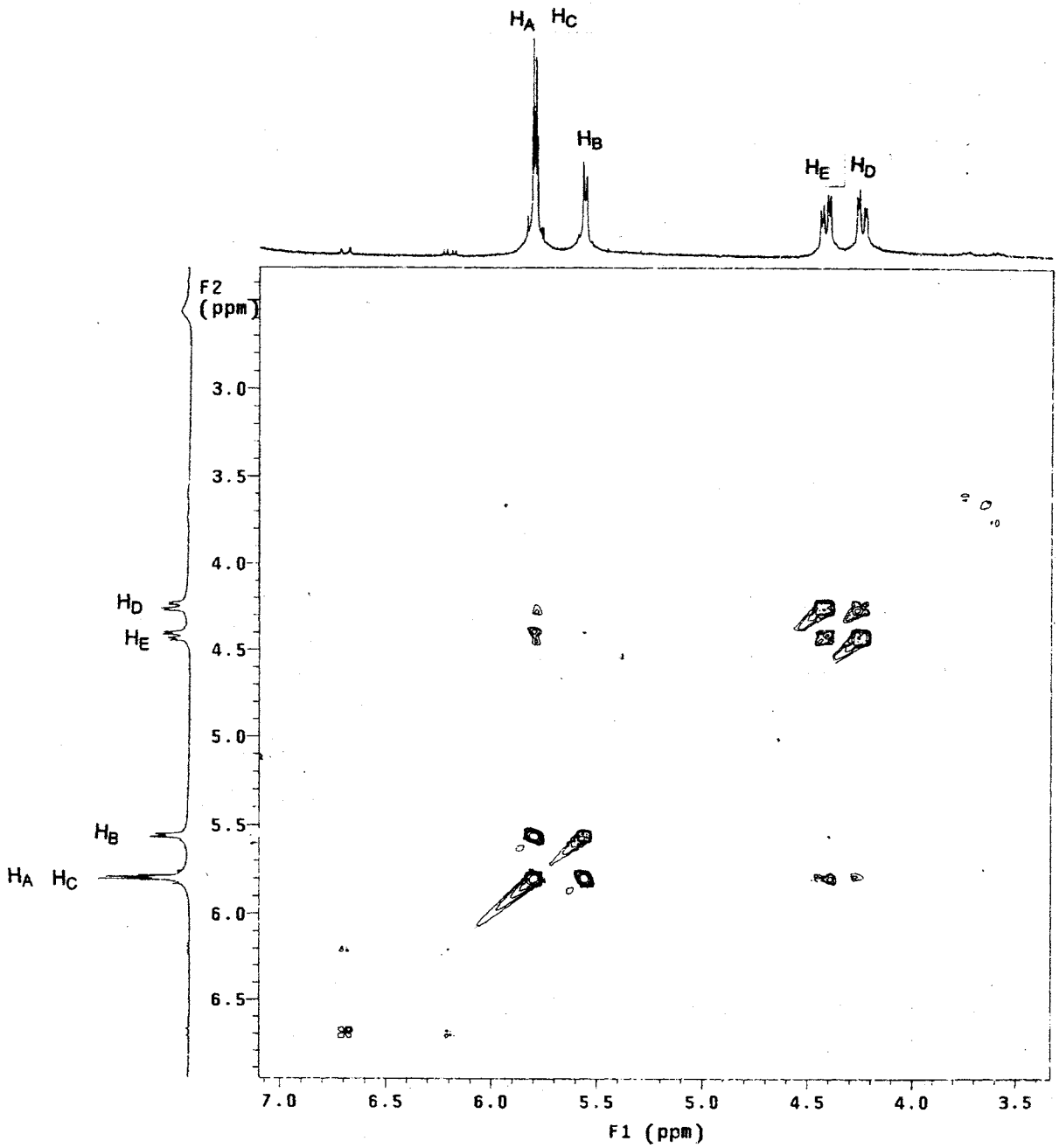
59.660
140
130
120
110
100
90
80
70
60
ppm

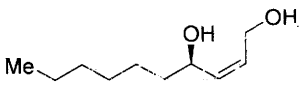
heb7-129-COSY

Pulse Sequence: COSY
Solvent: CDCl3
Ambient temperature
GEMINI-400BB "nmr8"

Relax. delay 1.000 sec
Acq. time 0.194 sec
Width 2640.7 Hz
2D Width 2640.7 Hz
200 repetitions
128 increments
OBSERVE H1, 400.0268158 MHz
DATA PROCESSING
Sq. sine bell 0.097 sec
F1 DATA PROCESSING
Sq. sine bell 0.048 sec
FT size 2048 x 2048
Total time 9 hr, 26 min, 5 sec





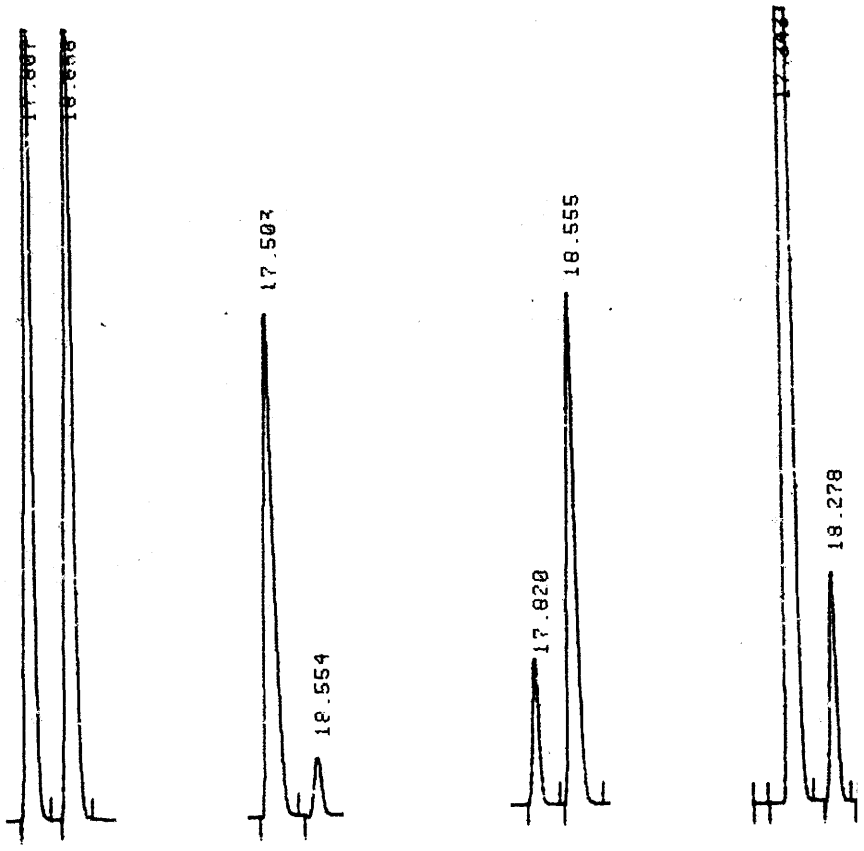


(*R,Z*)-Dec-2-ene-1,4-diol (Table 3.12, entry 2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 6.8 Hz, CH_3CH_2), 1.22-1.28 (8H, br s, $(CH_2)_4$), 1.30-1.46 (1H, m, $CH_2CH_AH_BCHOH$), 1.56-1.60 ($CH_2CH_AH_BCHOH$), 4.09 (1H, dd, J = 12.9, 5.6 Hz, $HOCH_AH_BC$), 4.30 (1H, dd, J = 13.2, 7.6 Hz, $HOCH_AH_BC$), 4.42 (1H, q, J = 7.0 Hz, CH_2CHOH), 5.54 (1H, dd, J = 11.2, 8.4 Hz, $CCHCHOH$), 5.70 (1H, ddd, J = 11.2, 7.6, 5.6 Hz, $CCHCH_2OH$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.7, 25.4, 29.3, 31.9, 37.5, 58.7, 67.9, 130.3, 135.5. IR (neat). 3314 (br s), 2955 (s), 2855 (s), 1459 (m), 1378 (m), 1018 (s) cm^{-1}. HRMS-(ESI+): for $C_{10}H_{20}O_2Na$ calc'd: 195.1361 $(M+Na)^+$, observed: 195.1372 $(M+Na)^+$. The unpurified reaction mixture was purified on silica gel with 50% ethyl acetate/hexanes as the eluant to afford a clear oil in 83% yield (31 mg). R_f = 0.16 (50% ethyl acetate, stain in PMA).

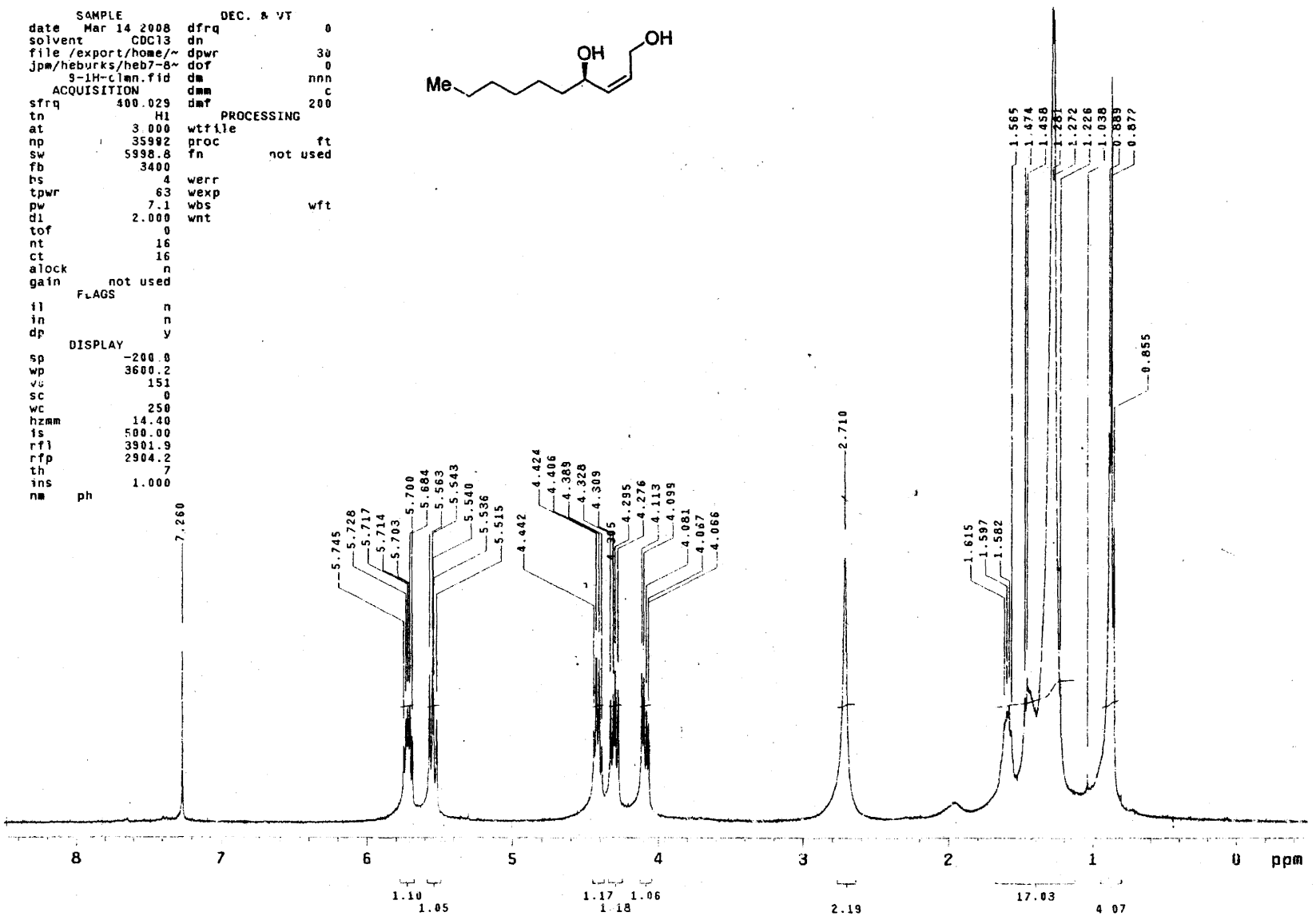
Proof of Configuration.

The 1,4-dihydroxylation product (*R,Z*)-dec-2-ene-1,4-diol was treated with ozone in the procedure described for (*R,Z*)-1-cyclohexylbut-2-ene-1,4-diol. The resulting 1,2-diol was treated with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid at 60 °C for 5 min. The unpurified mixture was passed through a silica gel plug with 10% ethyl acetate/hexanes as the eluant. The resultant ketal was compared to racemic ketal of octane-1,2-diol prepared from dihydroxylation of octene with osomium tetraoxide and 4-methyl morpholine N-oxide. The authentic sample was prepared from the Sharpless asymmetric dihydroxylation of octene utilizing AD-mix α.[36]

Chiral GLC (β-dex, Supelco, 100 °C) – analysis of the acetonide of octane-1,2-diol.



racemic | reaction product | authentic | reaction product and racemic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sw 5998.8
fb 3400
bs 4
tpwr 63
pw 7.1
d1 2.000
tof 0
nt 16
ct 16
alock n
gain not used
FLAGS
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in n
dp y
DISPLAY
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wc 250
hzmm 14.40
is 500.00
rfl 3901.9
rfp 2904.2
th 7
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nm ph
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dmf 200
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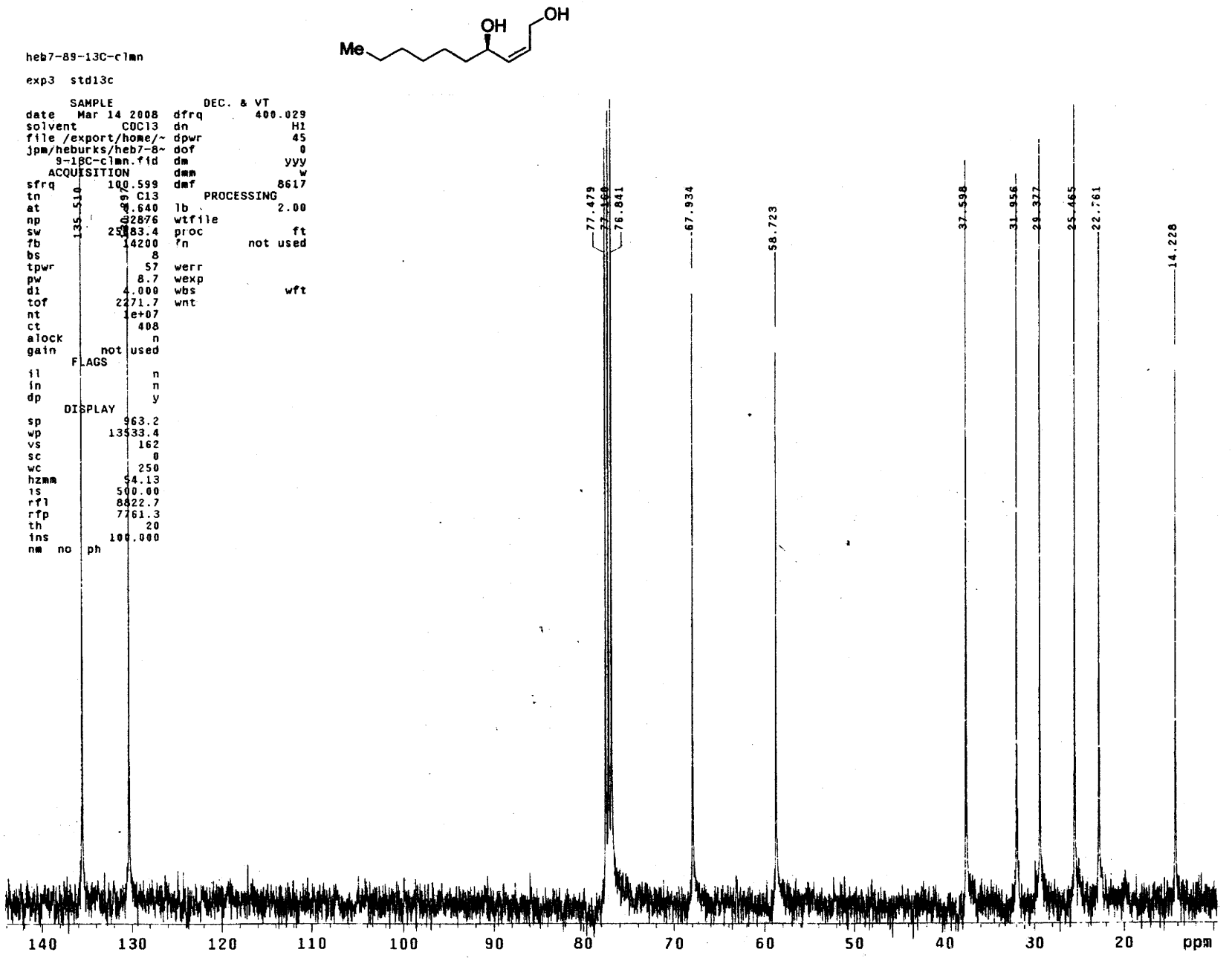
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gain not used
FLAGS
il n
in n
dp y
DISPLAY
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wc 250
hzmm 54.13
is 500.00
rfl 8822.7
rfp 7761.3
th 20
ins 100.000
nm no ph
DEC. & VT
dfrq 400.029
dn H1
dpwr 45
dof 0
dm yyy
dmm w
dmf 8617
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wexp
wbs wft
wnt
Me
OH
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37.598
31.956
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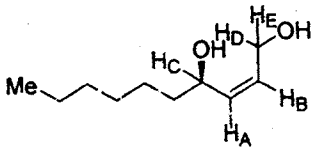
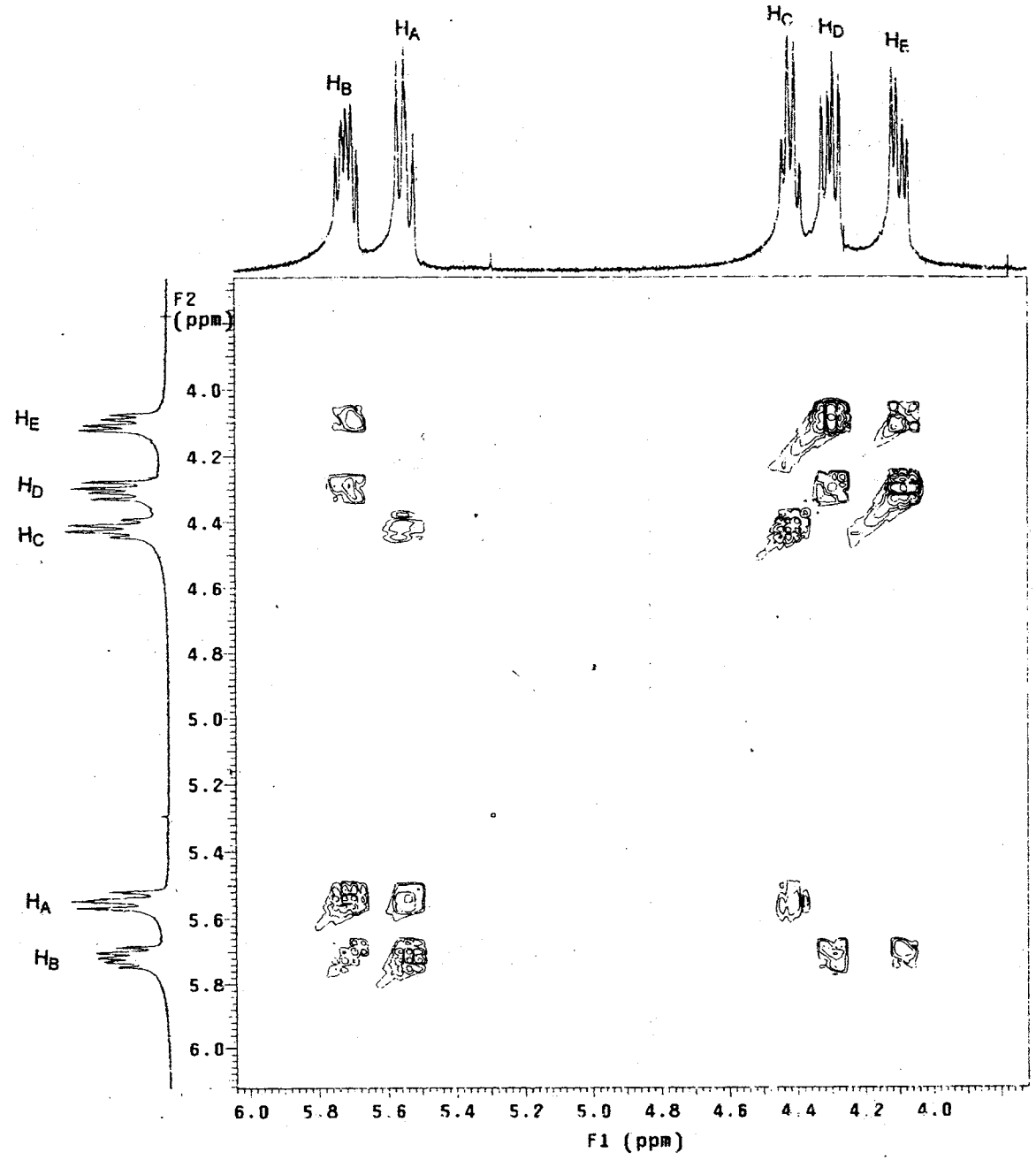
14.228
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

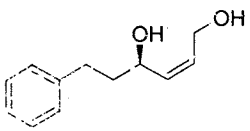
heb7-89-COSY

Pulse Sequence. COSY
Solvent: CDCl3
Ambient temperature
GEMINI-400BB "nmr8"

Relax. delay 1.000 sec
Acq. time 0.178 sec
Width 2877.2 Hz
20 Width 2877.2 Hz
150 repetitions
128 increments
OBSERVE H1, 400.0268146 MHz
DATA PROCESSING
Sq. sine bell 0.089 sec
F1 DATA PROCESSING
Sq. sine bell 0.044 sec
FT size 2048 x 2048
Total time 6 hr, 59 min, 9 sec





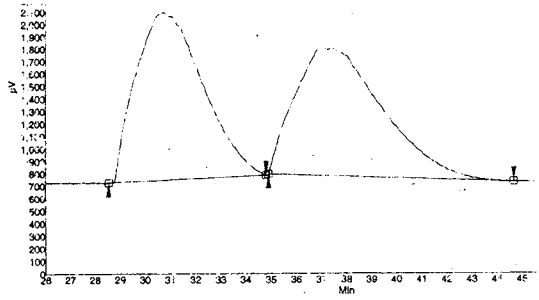


(*R,Z*)-6-Phenylhex-2-ene-1,4-diol (Table 3.12, entry 3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (1H, br s, O**H**), 1.75-2.01 (1H, br s, O**H**), 1.79 (1H, m, C$\mathbf{H_A}$H$_B$CHOH), 1.95 (1H, m, CH$_A$**H$_B$**CHOH), 2.69 (2H, m, PhC**H$_2$**), 4.13 (1H, dd, J = 13.2, 6 Hz, C$\mathbf{H_A}$H$_B$OH), 4.25 (1H, ddd, J = 13.2, 7.2, 1.6 Hz, CH$_A$**H$_B$**OH), 4.45 (1H, q, J = 7.0 Hz, C**H**OH), 5.62 (1H, ddt, J = 11.2, 8.0, 1.6 Hz, CHOHC**H**C), 5.75 (1H, ddd, J = 11.2, 7.2, 6 Hz, C**H**CH$_2$OH), 7.17-7.21 (2H, m, Ar**H**), 7.26-7.30 (3H, m, Ar**H**). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.8, 39.0, 58.9, 67.4, 126.0, 128 4, 128.5, 130.6, 135.1, 141.6. IR (neat): 3312 (br s), 3024 (m), 2925 (m), 2859 (m), 1453 (m), 1012 (s). 696 (s) cm^{-1}. HRMS-(ESI+): for $C_{12}H_{16}O_2Na$ calc'd: 215.1048 $(M+Na)^+$, observed: 215.1039 $(M+Na)^+$. The unpurified reaction mixture was purified on silica gel with 50% ethyl acetate/hexanes as the eluant to afford a clear oil in 78% yield (95 mg). R_f = 0.25 (50% ethyl acetate, stain in PMA).

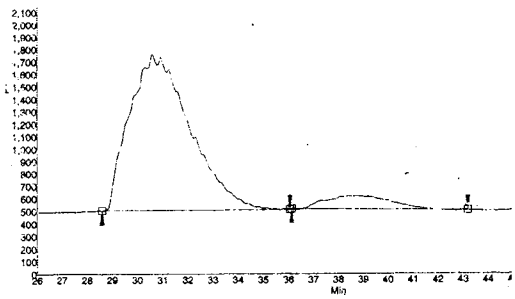
Proof of Configuration.

The 1,4-dihydroxylation product (*R,Z*)-6-phenylhex-2-ene-1,4-diol was treated with ozone in the procedure described for (*R,Z*)-1-cyclohexylbut-2-ene-1,4-diol. The resulting 1,2-diol was treated with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid at 60 °C for 5 min. The unpurified mixture was passed through a silica gel plug with 10% ethyl acetate/hexanes as the eluant. The resultant ketal was compared to racemic ketal of 4-phenyl-butane-1,2-diol prepared from dihydroxylation of 4-phenyl-1-butene with osomium tetraoxide and 4-methyl morpholine N-oxide.

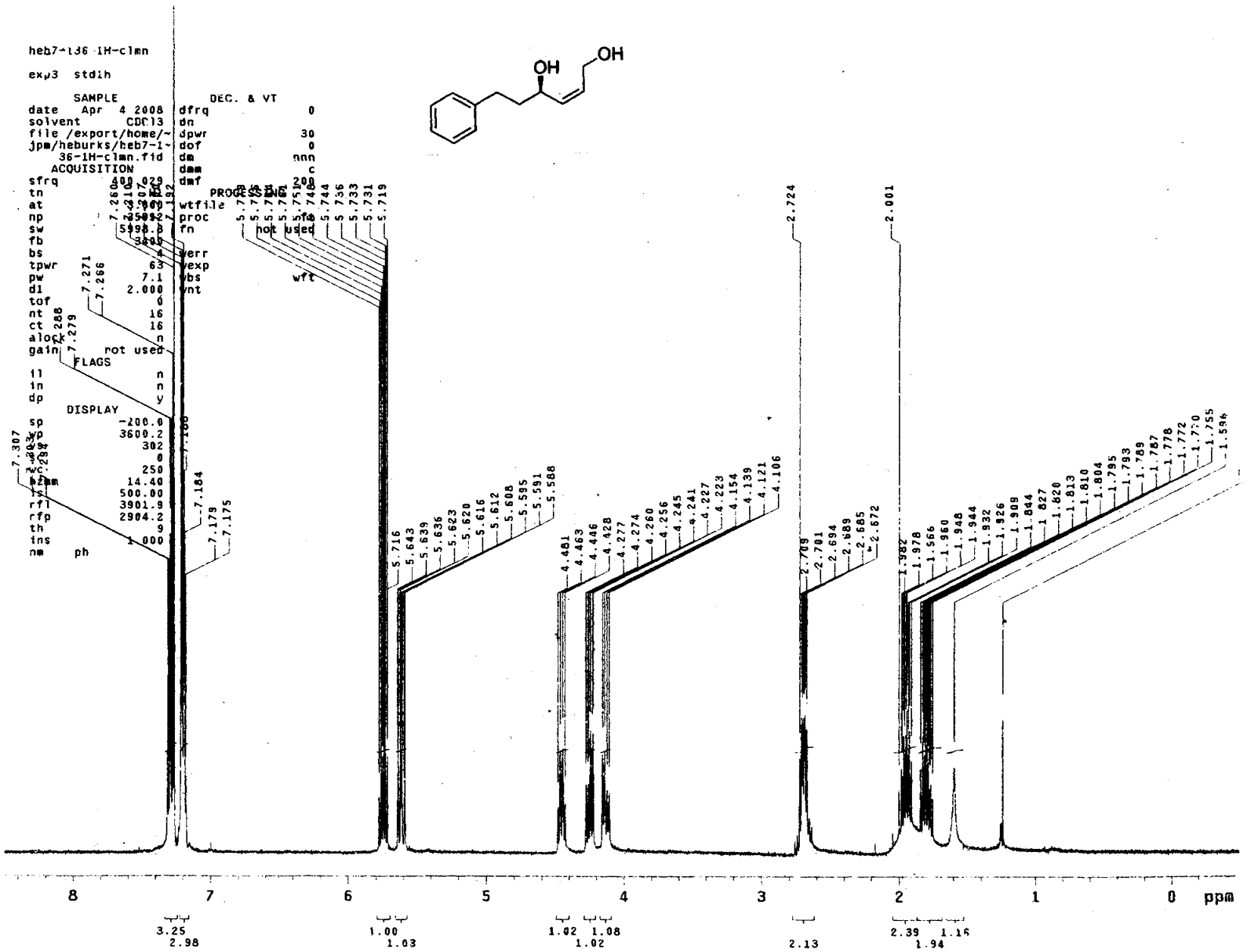
Chiral SFC (ODH, 1.5% MeOH, 4 mL/min) – analysis of the diol of 4-phenyl-butane-1,2-diol.



racemic



reaction product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date Apr 4 2008
solvent CDCl3
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jpm/heburks/heb7-1~
36-1H-clmn.fid
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at
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sw
fb
bs
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d1 2.000
tof 0
nt 16
ct 16
alock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -200.0
wp 3600.2
DEC. & VT
dfrq 0
dn
dpwr 30
dof 0
dm nnn
dmm c
dmf
PROCESSING
wtfile
proc wft
fn not used
werr
wexp
wbs
wnt
OH
OH
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7.294
7.288
7.279
7.271
7.266
7.184
7.179
7.175
5.768
5.761
5.751
5.748
5.744
5.736
5.733
5.731
5.719
5.716
5.643
5.639
5.636
5.623
5.620
5.616
5.612
5.608
5.595
5.591
5.588
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4.463
4.446
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4.274
4.260
4.256
4.245
4.241
4.227
4.223
4.154
4.139
4.121
4.106
2.724
2.709
2.701
2.694
2.689
2.685
2.672
2.001
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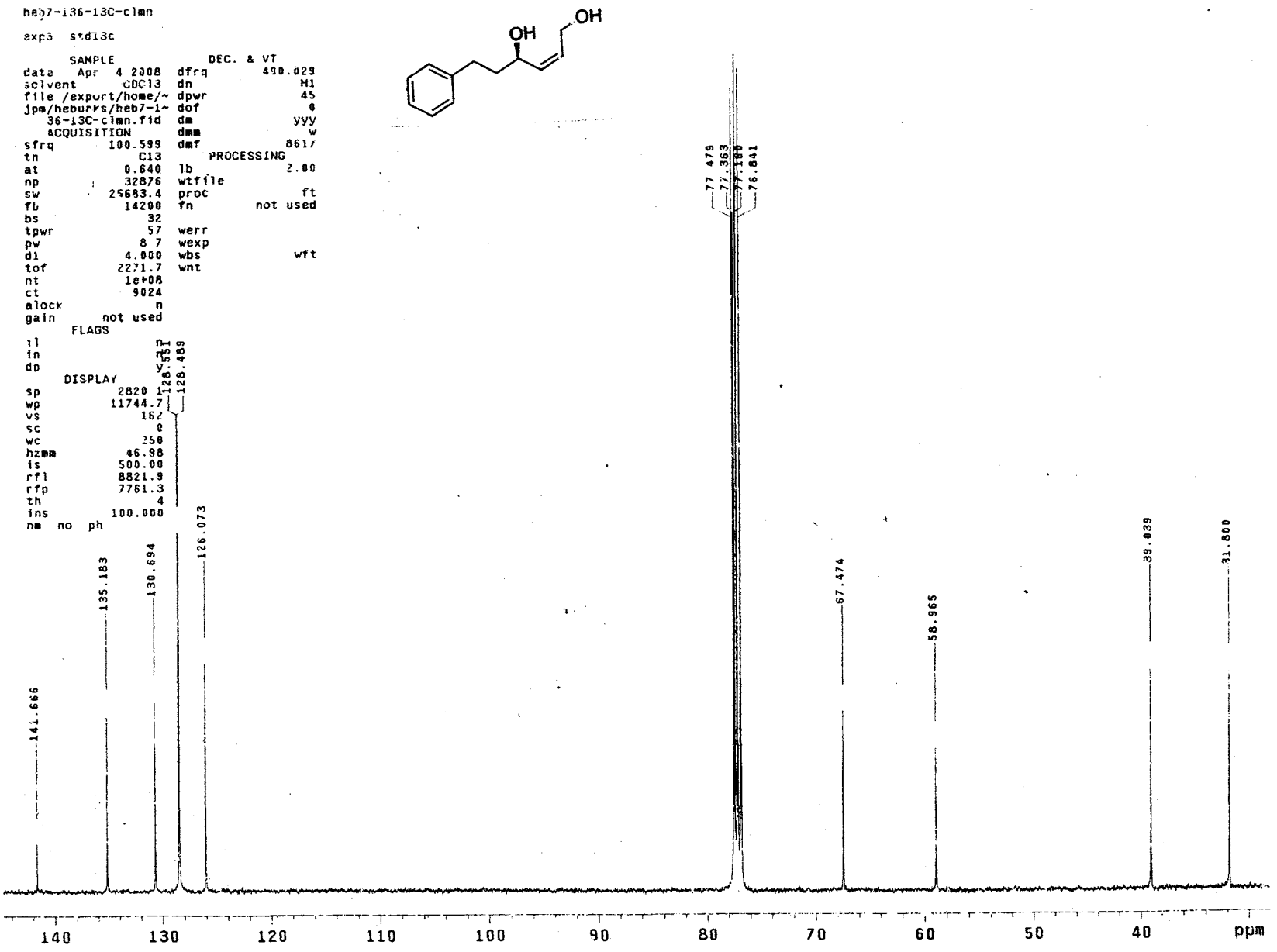
1.978
1.966
1.960
1.948
1.944
1.932
1.926
1.909
1.844
1.827
1.820
1.813
1.810
1.804
1.795
1.793
1.789
1.787
1.778
1.772
1.770
1.755
1.594
8
7
6
5
4
3
2
1
0
ppm
3.25
2.98
1.00
1.03
1.02
1.08
1.02
2.13
2.39
1.16
1.94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date Apr 4 2008
solvent CDCl3
file /export/home/~
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bs 32
tpwr 57
pw 8.7
d1 4.000
tof 2271.7
nt 1e+08
ct 9024
alock n
gain not used
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wp 11744.7
vs 162
sc 0
wc 250
hzmm 46.98
is 500.00
rfl 8821.9
rfp 7761.3
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ins 100.000
nm no ph
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dfrq 400.029
dn H1
dpwr 45
dof 0
dm yyy
dmm w
dmf 8617
PROCESSING
lb 2.00
wtfile
proc ft
fn not used
werr
wexp
wbs wft
wnt
OH
OH
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77.363
77.160
76.841
128.551
128.489
144.666
135.183
130.694
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31.800
140
130
120
110
100
90
80
70
60
50
40
ppm

heb7-147-1H-COSY

Pulse Sequence: COSY
Solvent: CDCl3
Ambient temperature
File: heb7-147-COSY
GEMINI-400BB "nmr8"

Relax. delay 1.000 sec
Acq. time 0.195 sec
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20 Width 2625.0 Hz
90 repetitions
300 increments
OBSERVE H1, 400.0268509 MHz
DATA PROCESSING
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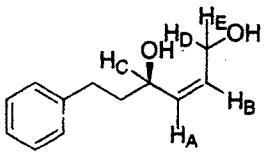
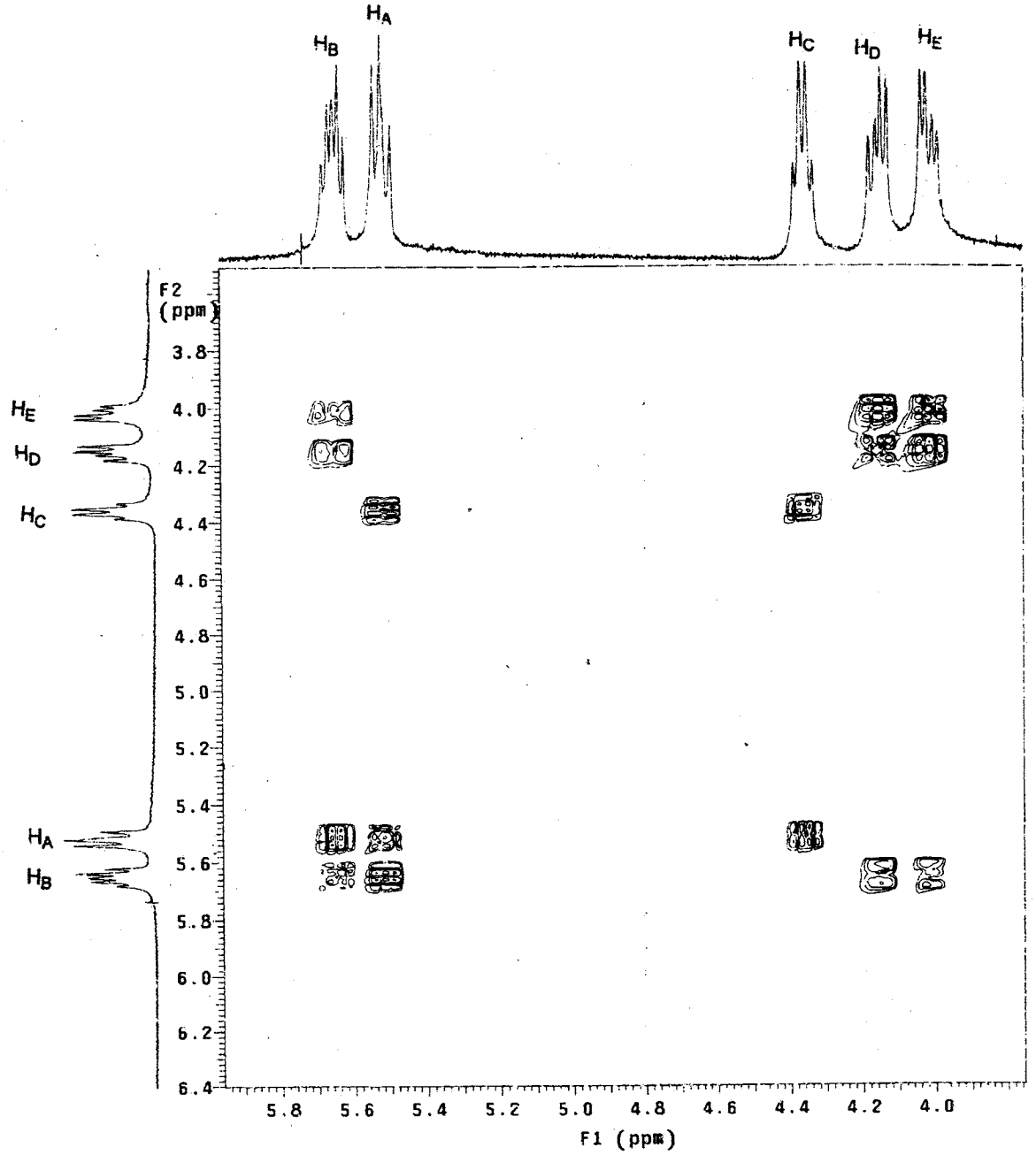
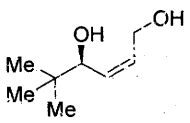
F1 DATA PROCESSING
Sq. sine bell 0.049 sec
FT size 4096 x 4096
Total time 10 hr, 13 min, 7 sec





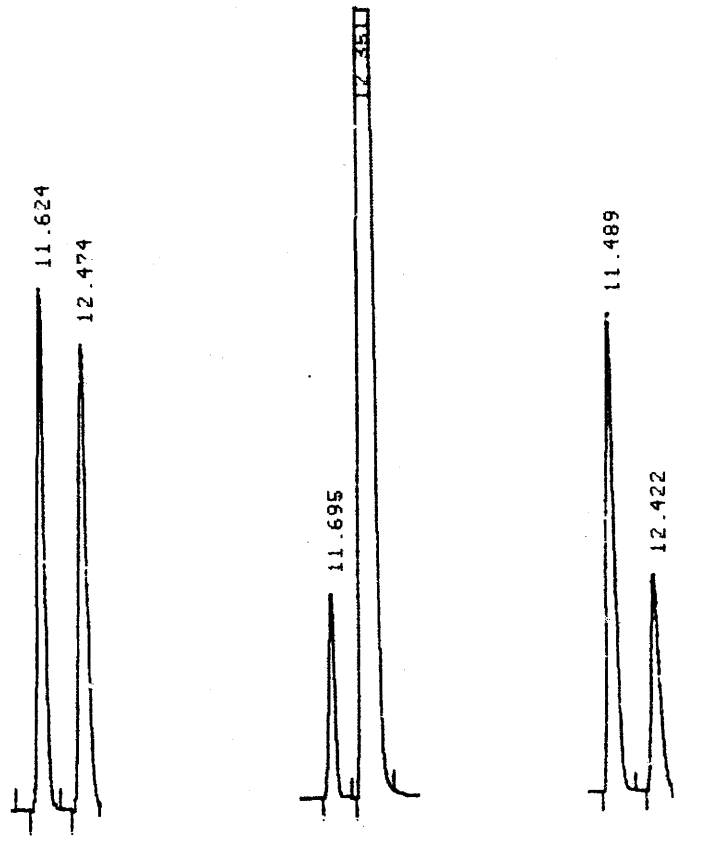


(*S,Z*)-5,5-Dimethylhex-2-ene-1,4-diol (Table 3.12, entry 5). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (9H, s, $(C\mathbf{H_3})_3C$), 4.08 (1H, dd, J = 9.0, 1.0 Hz, $(CH_3)_3C\mathbf{H}$), 4.16 (1H, dd, J = 13.2, 5.5 Hz, $CHC\mathbf{H_A}H_BOH$), 4.33 (1H, ddd, J = 13.2, 7.5, 1.5 Hz, $CHCH_A\mathbf{H_B}OH$), 5.62 (1H, ddt, J = 11.5, 9.0, 1.3 Hz, $C\mathbf{H}CHCH_2OH$), 5.78-5.83 (1H, m, $CHC\mathbf{H}CH_2OH$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 35.1, 59.0, 75.4, 131.7, 132.0. IR (neat): 3340 (s), 2955 (s), 2907 (s), 2870 (s), 1478 (m), 1463 (m), 1392 (m), 1363 (m), 1030 (s), 1001 (s) cm^{-1}. HRMS-(ESI+): for $C_8H_{16}O_2Na$ calc'd: 167.1048 $(M+Na)^+$, observed: 167.1053 $(M+Na)^+$. The unpurified reaction mixture was purified on silica gel with 50% ethyl acetate/hexanes as the eluant to afford a clear oil in 26% yield (13 mg). R_f = 0.22 (50% ethyl acetate, stain in PMA).

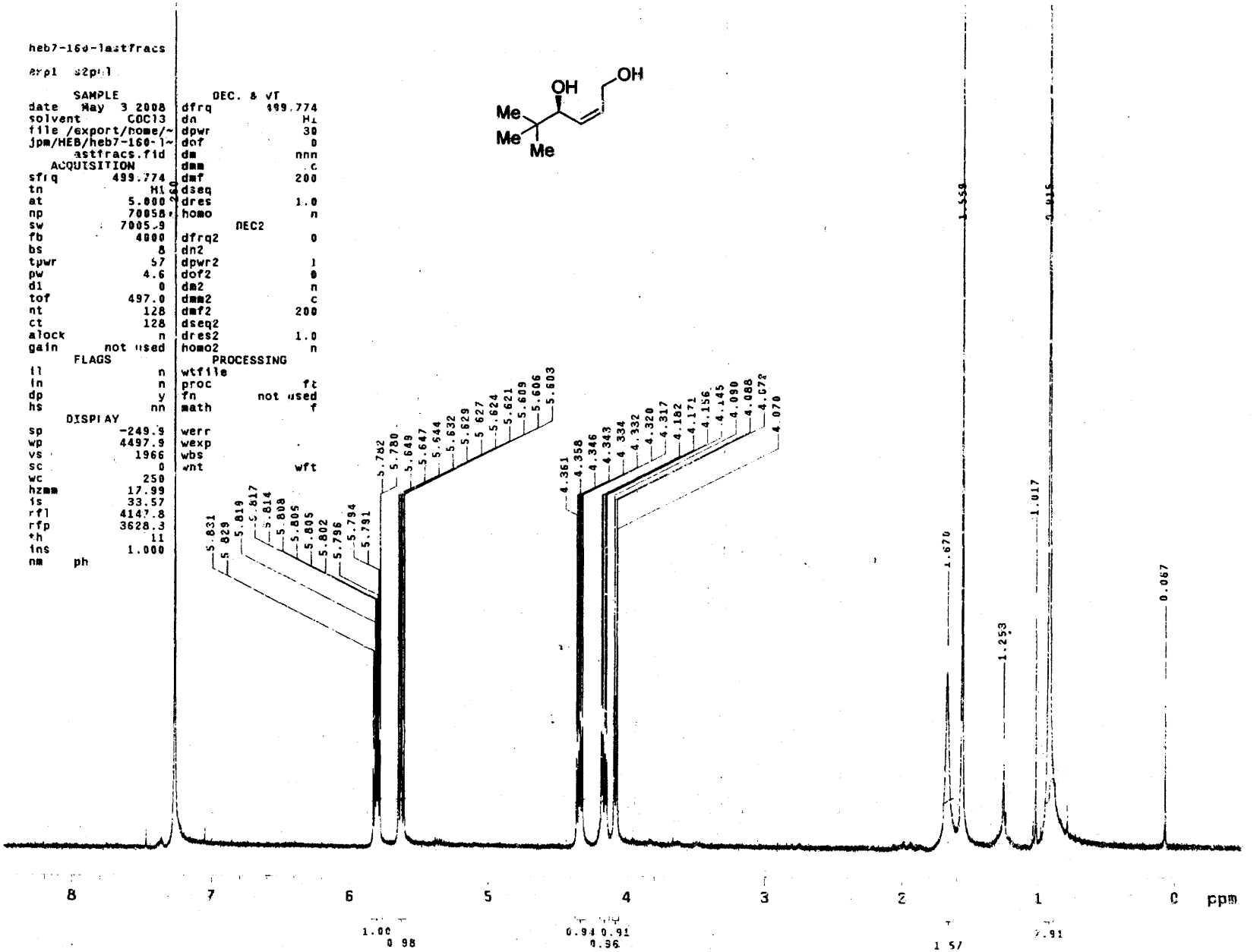
Proof of Configuration.

The 1,4-dihydroxylation product (*S,Z*)-5,5-dimethylhex-2-ene-1,4-diol was treated with ozone in the procedure described for (*R,Z*)-1-cyclohexylbut-2-ene-1,4-diol. The resulting 1,2-diol was treated with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid at 60 °C for 5 min. The unpurified mixture was passed through a silica gel plug with 10% ethyl acetate/hexanes as the eluant. The resultant ketal was compared to racemic ketal of 3,3-dimethylbutane-1,2-diol prepared from dihydroxylation of 3,3-dimethyl-1-butene with osomium tetraoxide and 4-methyl morpholine N-oxide. The authentic sample was prepared from the Sharpless asymmetric dihydroxylation of 3,3-dimethyl-1-butene utilizing AD-mix α.[36]

Chiral GLC (β-dex, Supelco, 75 °C) – analysis of the acetonide of 3,3-dimethylbutane-1,2-diol.



racemic reaction product authentic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fb 4000
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tpwr 57
pw 4.6
d1 0
tof 497.0
nt 128
ct 128
alock n
gain not used
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in n
dp y
hs nn
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wp 4497.9
vs 1966
sc 0
wc 250
hzmm 17.99
is 33.57
rfl 4147.8
rfp 3628.3
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ins 1.000
nm ph
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dmf 200
dseq
dres 1.0
homo n
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dn2
dpwr2 1
dof2 0
dm2 n
dmm2 c
dmf2 200
dseq2
dres2 1.0
homo2 n
PROCESSING
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proc ft
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5.805
5.805
5.802
5.796
5.794
5.791
5.782
5.780
5.649
5.647
5.644
5.632
5.629
5.627
5.624
5.621
5.609
5.606
5.603
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4.334
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4.171
4.156
4.145
4.090
4.088
4.072
4.070
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1.253
1.017
0.915
0.067
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7
6
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0
ppm
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0.91
0.96
1.57
2.91

heb7-160-13C-clmn

exp1 s2pul

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tn	C13	dseq	
at	3.000	dres	1.0
np	200168	homo	n
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fb	18000	dfrq2	0
bs	32	dn2	
tpwr	55	dpwr2	1
pw	7.0	dof2	0
d1	2.000	dm2	n
tof	818.6	dmm2	c
nt	1e+08	dmf2	10000
ct	1472	dseq2	
alock	n	dres2	1.0
gain	not used	homo2	n
FLAGS		PROCESSING	
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in	n	wtfile	
dp	y	proc	ft
hs	nn	fn	not used
DISPLAY		math	f
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wp	14422.7	werr	
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rfp	0	wbs	wft
th	250	wnt	
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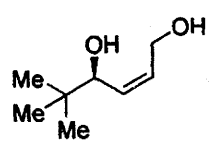
rfp	9696.5		
th	19		
ins	100.000		
nm	cdc ph		



heb7-122-COSY

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Ambient temperature
File: heb7-122-COSY
GEMINI-400BB "nmr8"

Relax. delay 1.000 sec
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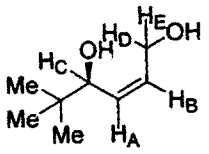
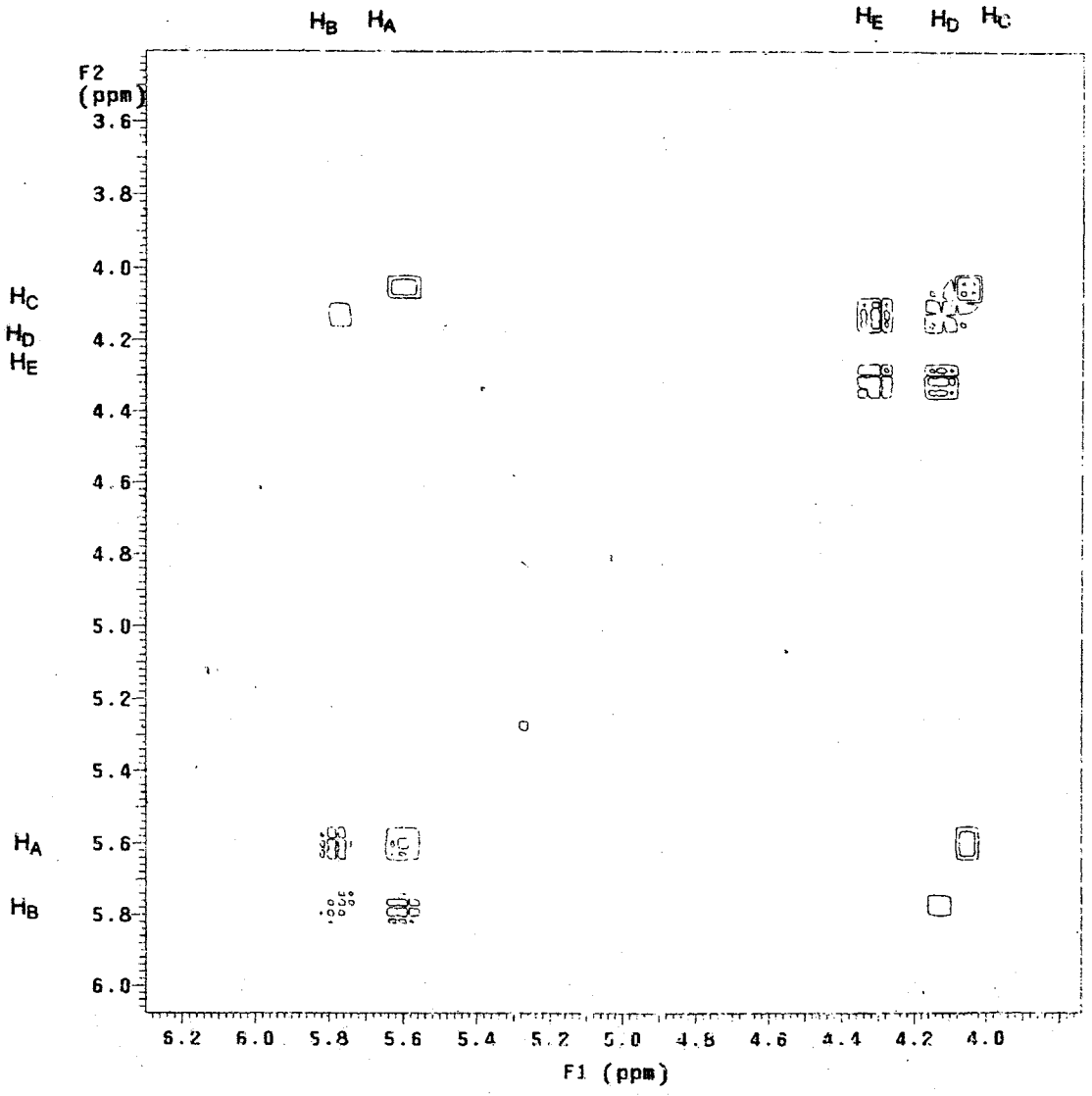
2D Width 5998.8 Hz
100 repetitions
260 increments
OBSERVE H1, 400.0268234 MHz
DATA PROCESSING
Sq. sine bell 0.085 sec
F1 DATA PROCESSING
Sq. sine bell 0.021 sec
FT size 4096 x 4096
Total time 9 hr, 30 min, 19 sec





3.5.11. Diboration of cis-Piperylene.

The diboration of *cis*-piperylene was conducted according to the general procedure in Section 3.5.5.

3.5.12. Diboration of 1,3-Cyclohexadiene

In the dry box, to an 6-dram vial equipped with a magnetic stir bar was added $Pt_2(dba)_3$ (10.2 mg, 0.0093 mmol), tricyclohexylphosphine (6.3 mg, 0.0224 mmol), and toluene (3.7 mL, 0.1 M). The metal and ligand were complexed for 1 h, at which time the reaction mixture was charged with $B_2(pin)_2$ (99.7 mg, 0.3927 mmol) and 1,3-cyclohexadiene (30 mg, 0.374 mmol). The reaction mixture was sealed with a polypropylene cap, the cap was sealed with electrical tape, and the vial was removed from the glove box. The reaction mixture was allowed to stir at 60 °C for 14 h. The reaction mixture was cooled to ambient temperature and solvent was removed *in vacuo*. The unpurified reaction mixture was purified by column chromatography to afford 80 mg (64% yield) of a clear oil. Spectral data are in accordance with similar compounds reported in the literature.[8]